





60

5	S	8	10	15
	Glu Lys Ile Arg Leu Arg Pro Gly Gly Lys Lys Tyr Iys Leu Lys			
	28	28	28	28
10	His Ile Val Trp Ala Ser Arg Glu Leu Gln Arg Phe Ala Val Asn Pro			
	28	48	48	48
15	Gly Leu Leu Glu Thr Ser Ser Glu Gly Cys Arg Glu Ile Leu Gly Gln Leu			
	58	58	68	68
20	Gln Pro Ser Leu Gln Thr Gly Ser Glu Glu Leu Arg Ser Leu Tyr Asn			
	68	78	78	88
25	Thr Val Ala Thr Ieu Tyr Cys Val His Gln Arg Ile Glu Ile Lys Asp			
	88	98	98	98
30	Thr Lys Glu Ala Leu Asp Lys Ile Glu Glu Gln Asn Lys Ser Lys			
	108	108	118	118
35	Lys Lys Ala Gln Gln Ala Ala Ala Asp Thr Gly His Ser Asn Gln Val			
	118	128	128	138
40	Ser Gln Asn Tyr Pro Ile Val Gln Asn Ile Gln Gly Gln Met Val His			
	138	138	148	148
45	Gln Ala Ile Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Val Gln			
	148	158	158	168
50	Gln Lys Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser			
	168	178	178	178
55	Gln Gly Ala Thr Pro Gln Asp Ieu Asn Thr Met Ieu Asn Thr Val Gly			
	178	188	188	198
60	Gly His Gln Ala Ala Met Gln Met Leu Lys Glu Thr Ile Asn Gln Glu			
	198	208	208	208
65	Ala Ala Gln Trp Asp Arg Val His Pro Val His Ala Gly Pro Ile Ala			
	218	228	228	238
70	Pro Gly Gln Met Arg Gln Pro Arg Gly Ser Asp Ile Ala Gly Thr Thr			
	238	238	238	248
75	Ser Thr Ieu Gln Glu Glu Ile Gly Trp Met Thr Asn Asn Pro Ile			
	248	258	258	258
80	Pro Val Gly Glu Ile Tyr Iys Arg Trp Ile Ile Ieu Gly Leu Asn Iys			
	268	268	268	278
85	Ile Val Arg Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly			

81

	278	280	285
5	Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr Ieu 286 288 289		
10	Arg Ala Glu Gln Ala Ser Glu Glu Val Lys Asn Trp Met Thr Glu Thr 308 310 312 314		
15	Lys Leu Val Gln Asn Ala Asn Pro Asp Cys Lys Thr Ile Iys Iys Ala 326 330 335		
20	Leu Gly Pro Ala Ala Thr Leu Glu Glu Met Met Thr Ala Cys Gln Gly 346 348 350		
25	Val Gly Gly Pro Gly His Lys Ala Arg Val Leu Met Gly Pro Ile Ser 358 360 368		
30	Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro 370 378 380		
35	Iys Val Lys Glu Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val 388 390 392 400		
40	Gln Ile Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly 408 410 412		
45	Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp 420 428 430		
50	Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg 438 440 442		
55	Thr Glu Asp Phe Trp Glu Val Glu Leu Gly Ile Pro Asn Pro Ala Gly 450 452 454		
60	Leu Lys Lys Lys Ser Val Thr Val Leu Asp Val Gly Asp Ala Tyr 468 470 472 474		
65	Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr 488 490 492 494		
70	Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Glu Tyr Asn 508 510 512		
75	Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser 518 520 522		
80	Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Glu Asn Pro Asp Ile Val 538 538 540		
85	Ile Tyr Glu Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Ile Glu Ile		

## 82

5	S&S	S&S	S&S	S&S
	Gly Glu His Arg Thr Lys Ile Glu Glu Leu Arg Glu His Leu Leu Arg			
	626	678	678	
10	Trp Gly Ieu Thr Thr Pro Asp Lys Lys His Glu Iys Glu Pro Pro Phe			
	580	585	585	
	Leu Iys Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Glu Pro			
	595	600	600	
15	Ile Val Leu Pro Glu Iys Asp Ser Thr Val Asn Asp Ile Glu Lys			
	610	615	620	
20	Leu Val Gly Iys Leu Asn Trp Ala Ser Glu Ile Tyr Pro Gly Ile Lys			
	625	630	640	
25	Val Arg Glu Leu Cys Iys Leu Ieu Arg Gly Thr Iys Ala Leu Thr Glu			
	645	650	655	
30	Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg			
	660	665	670	
	Glu Ile Leu Iys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys			
	675	680	685	
35	Asp Leu Ile Ala Glu Ile Glu Iys Glu Gly Glu Glu Ile Trp Thr Tyr			
	690	695	700	
40	Glu Ile Tyr Glu Glu Pro Phe Lys Asn Leu Lys Thr Gly Iys Tyr Ala			
	705	710	720	
45	Arg Met Arg Gly Ala His Thr Asn Asp Val Lys Glu Leu Thr Glu Ala			
	725	730	735	
50	Val Glu Iys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Iys Thr Pro			
	740	745	750	
	Lys Phe Iys Leu Pro Ile Glu Iys Glu Thr Trp Glu Thr Trp Trp Thr			
	755	760	765	
55	Glu Tyr Trp Glu Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr			
	770	775	780	
60	Pro Pro Leu Val Iys Leu Trp Tyr Glu Leu Glu Lys Glu Pro Ile Val			
	785	790	800	
65	Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Iys			
	805	810	815	
	Leu Gly Iys Ala Gly Tyr Val Thr Asn Arg Asp Asp Glu Lys Val Val			

83

	830	835	840
5	The Leu Thr Asp Thr Thr Asn Glu Lys Thr Glu Leu Glu Ala Ile Tyr 819                    840                    845		
10	Leu Ala Leu Glu Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser 850                    855                    860		
15	Gln Tyr Ala Leu Gly Ile Ile Gln Ala Glu Pro Asp Glu Ser Glu Ser 865                    870                    875                    880		
20	Glu Leu Val Asn Glu Ile Ile Glu Glu Leu Ile Lys Lys Glu Lys Val 885                    890                    895		
25	Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Glu 895                    905                    910		
30	Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Met Val Gly 915                    920                    925		
35	Phe Pro Val Thr Pro Glu Val Pro Leu Arg Pro Met Thr Tyr Lys Ala 930                    935                    940		
40	Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Leu Glu Gly 945                    950                    955                    960		
45	Ile Ile His Ser Glu Arg Arg Glu Asp Ile Leu Asp Leu Trp Ile Tyr 965                    970                    975		
50	His Thr Glu Gly Tyr Phe Pro Asp Trp Glu Asn Tyr Thr Pro Gly Pro 980                    985                    990		
55	Gly Val Arg Tyr Pro Leu Thr Phe Gly Trp Cys Tyr Lys Leu Val Pro 995                    1000                    1005		
60	Val Glu Pro Asp Lys Val Glu Glu Ala Asn Lys Gly Glu Asn Thr 1010                    1015                    1020		
65	Ser Ile Leu His Pro Val Ser Leu His Gly Met Asp Asp Pro Glu 1025                    1030                    1035		
70	Arg Glu Val Leu Glu Trp Arg Phe Asp Ser Arg Leu Ala Phe His 1040                    1045                    1050		
75	His Val Ala Arg Glu Leu His Pro Glu Tyr Phe Lys Asn Cys 1055                    1060                    1065		
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	cggtggggcc cgggggggggg ggggggggggg ggggggggggg ggggggggggg ggggggggg	4320
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	tgggggggggg accgggggggg ggccgggggggg ggggggggggg ggggggggggg ggggggggg	4440
15	gtgggggttcg ccctggggcc tttgggggggggg tttttttttt ggggggggggg ggggggggg	4500
	gggggggggggg ggggggggggg ggggggggggg ggggggggggg ggggggggggg ggggggggg	4560
	atgg	4620
20	cacagg	4680
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	<221> PRY	
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	<400> 4	
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	20 28 36	
	His Leu Val Trp Ala Ser Arg Glu Leu Asp Arg Phe Ala Leu Asn Pro	
40	35 43 45	
	Ser Leu Leu Glu Thr Thr Glu Gly Cys Gln Ile Met Asn Glu Leu	
	50 58 68	
45	Gln Pro Ala Val Lys Thr Gly Thr Glu Glu Ile Lys Ser Leu Phe Asn	
	65 73 75 83	
50	Tyr Val Ala Thr Leu Tyr Cys Val His Glu Arg Ile Asp Val Lys Asp	
	85 93 95	
55	Tyr Lys Glu Ala Leu Asp Lys Ile Glu Glu Ile Glu Asn Lys Ser Lys	
	105 108 110	
60	Gln Lys Thr Gln Gln Ala Ala Asp Thr Gly Asp Ser Ser Lys Val	
	118 120 128	
	Ser Gln Asn Tyr Pro Ile Ile Gln Asn Ala Gln Gly Gln Met Ile His	
	138 138 140	
65	Gln Asn Leu Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Ile Glu	
	148 150 152 160	

168 Lys Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser  
 169 170 171

5

Gly Gly Glu Thr Pro Gln Asp Leu Asn Val Met Leu Asn Ile Val Gly  
 188 189 190

10

Gly His Glu Ala Ala Met Glu Met Leu Lys Asp Thr Ile Asn Glu Glu  
 191 192 193

15

Ala Asn Glu Trp Asp Arg Leu His Pro Val Gln Ala Gly Pro Ile Pro  
 210 211 212

20

Pro Gly Glu Ile Arg Glu Pro Arg Gly Ser Asp Ile Ala Gly Thr Thr  
 228 229 230 231 232 233 234 235 236

25

Ser Thr Pro Glu Glu Glu Leu Glu Trp Met Thr Gly Asn Pro Pro Ile  
 248 249 250 251 252 253

30

Ile Val Arg Met Tyr Ser Pro Val Ser Ile Leu Asp Ile Lys Glu Gly  
 278 279 280 281

35

Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Phe Lys Ala Leu  
 298 300 301 302

40

Arg Ala Glu Glu Ala Thr Gln Asp Val Lys Gly Trp Met Thr Glu Thr  
 328 329 330 331 332 333

45

Leu Leu Val Glu Asn Ala Asn Pro Asp Cys Lys Ser Ile Leu Lys Ala  
 358 359 360 361 362

50

Leu Gly Ser Gly Ala Thr Leu Glu Met Met Thr Ala Cys Glu Gly  
 388 389 390 391 392

55

Gln Ala Glu Glu Thr Asn Ile Met Met Gln Arg Gly Asn Phe Arg Gly  
 398 400 401 402

60

Gln Lys Arg Ile Lys Cys Phe Asn Cys Gly Lys Glu Gly His Leu Ala  
 428 429 430 431 432

65

Arg Asn Cys Arg Ala Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys  
 468 469 470 471 472 473

Glu Gly His Glu Met Lys Asp Cys Thr Gln Arg Glu Ala Asn Phe Leu  
 488 489 490 491 492

68

Gly Lys Ile Trp Pro Ser Ser Lys Gly Arg Pro Gly Asn Phe Pro Gln  
 438 440 442  
 5 Ser Arg Pro Glu Pro Thr Ala Pro Pro Ala Glu Leu Phe Gly Met Gly  
 450 452 454  
 10 Glu Gly Ile Ala Ser Leu Pro Lys Glu Gln Lys Asp Arg Gln Gln  
 465 470 475 480  
 15 Val Pro Pro Leu Val Ser Leu Lys Ser Leu Phe Gly Asn Asp Pro Leu  
 485 490 495  
 20 Ser Gln Gly Ser Pro Ile Ser Pro Ile Glu Thr Val Pro Val Thr Leu  
 500 505 510  
 25 Lys Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Gln  
 515 520 525  
 30 Glu Lys Ile Lys Ala Leu Thr Glu Ile Cys Thr Gln Met Gln Lys Glu  
 530 535 540  
 35 Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp  
 555 560 565  
 40 Phe Arg Gln Leu Asn Lys Arg Thr Gln Asp Phe Trp Gln Val Gln Leu  
 580 585 590  
 45 Gly Ile Pro Gln Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val  
 600 605 610  
 50 Leu Asp Val Gln Asp Ala Tyr Phe Ser Val Pro Leu Asp Gln Asn Phe  
 620 625 630  
 55 Arg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Gln Thr Pro  
 645 650 655  
 60 Gly Val Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gln Ser  
 675 680 685  
 65 Pro Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Gln Pro Phe Arg  
 690 695 700  
 Ser Lys Asn Pro Glu Ile Ile Tyr Gln Tyr Met Ala Ala Leu Tyr  
 725 730 735  
 70 Val Gln Ser Asp Leu Gln Ile Gln Gln His Arg Thr Lys Ile Gln Gln  
 750 755 760

Leu Arg Ala His Leu Leu Ser Trp Gly Phe Thr Thr Pro Asp Lys Lys  
 703 713 723

5 His Glu Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Ileu His Pro  
 725 735 745

10 Asp Lys Tyr Thr Val Glu Pro Ile Met Leu Pro Asp Lys Glu Ser Trp  
 745 755 765

15 Thr Val Asn Asp Ile Glu Iys Leu Val Gly Iys Leu Asn Trp Ala Ser  
 765 775 785

Gln Ile Tyr Ala Gly Ile Iys Val Iys Gln Leu Cys Arg Iea Leu Arg  
 775 785 795

20 Gly Ala Iys Ala Leu Thr Asp Ile Val Thr Leu Thr Glu Glu Ala Glu  
 795 805 815

25 Leu Glu Leu Ala Glu Asn Arg Glu Ile Leu Lys Asp Pro Val His Glu  
 805 815 825

30 Val Tyr Tyr Asp Pro Ser Lys Asp Leu Val Ala Glu Ile Glu Iys Gln  
 825 835 845

35 Gly Glu Asp Glu Trp Thr Tyr Gln Ile Tyr Glu Glu Pro Phe Iys Asn  
 845 855 865

40 Leu Iys Thr Gly Iys Tyr Ala Arg Iys Arg Ser Ala His Thr Asn Asp  
 865 885 895

Val Arg Glu Leu Ala Glu Val Val Glu Iys Val Ala Met Glu Ser Ile  
 895 905 915

45 Val Ile Trp Gly Iys Thr Pro Iys Phe Iys Leu Pro Ile Glu Iys Glu  
 905 915 925

50 Thr Trp Glu Thr Trp Trp Met Asp Tyr Trp Gln Ala Thr Trp Ile Pro  
 925 935 945

55 Glu Trp Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Glu  
 945 955 965

60 Leu Glu Iys Asp Pro Ile Leu Gly Ala Glu Thr Phe Tyr Val Asp Gly  
 965 975 985

Ala Ala Asn Arg Glu Thr Iys Leu Gly Iys Ala Gly Tyr Val Thr Asp  
 985 995 1005

65 Arg Gly Arg Glu Lys Val Val Ser Leu Thr Glu Thr Thr Asn Glu Iys  
 1005 1015 1025

Thr Glu Leu His Ala Ile Leu Leu Ala Leu Glu Asp Ser Gly Ser Glu  
 580 585 590

5 Val Asn Ile Val Thr Asp Ser Glu Tyr Ala Leu Gly Ile Ile Glu Ala  
 595 1000 1005

10 Glu Pro Asp Arg Ser Glu Ser Glu Leu Val Asn Glu Ile Ile Glu  
 1010 1015 1020

15 Lys Leu Ile Gly Lys Asp Iys Ile Tyr Leu Ser Trp Val Pro Ala  
 1025 1030 1035

20 His Lys Gly Ile Gly Gly Asn Glu Glu Val Asp Lys Leu Val Ser  
 1040 1045 1050

25 Ser Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile Asp Lys Ala  
 1055 1060 1065

30 Glu Glu Asp His Glu Arg Tyr His Ser Asn Trp Arg Thr Met Ala  
 1070 1075 1080

35 Ser Asp Phe Asn Leu Pro Pro Ile Val Ala Lys Glu Ile Val Ala  
 1085 1090 1095

40 Ser Cys Asp Lys Cys Glu Leu Lys Gly Glu Ala Met His Gly Glu  
 1100 1105 1110

45 Val Asp Cys Ser Pro Gly Ile Trp Glu Leu Ala Cys Thr His Leu  
 1115 1120 1125

50 His Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr  
 1130 1135 1140

55 Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly Glu Glu Thr Ala  
 1145 1150 1155

60 Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Val Val  
 1160 1165 1170

65 His Thr Ala Asn Gly Ser Asn Phe Thr Ser Ala Ala Val Lys Ala  
 1175 1180 1185

70 Ala Cys Trp Trp Ala Asn Ile Glu Glu Phe Gly Ile Pro Tyr  
 1190 1195 1200

75 Asn Pro Glu Ser Glu Gly Val Val Ala Ser Met Asn Lys Glu Leu  
 1205 1210 1215

80 Lys Lys Ile Ile Gly Glu Val Arg Asp Glu Ala Glu His Leu Lys  
 1220 1225 1230

Thr Ala Val Glu Met Ala Val Phe Ile His Asn Phe Lys Arg Lys  
 1238 1242 1245  
**5**  
 Gly Gly Ile Gly Gly Tyr Ser Ala Gly Gln Arg Ile Ile Asp Ile  
 1250 1255 1260  
**10** Ile Ala Thr Asp Ile Gln Thr Lys Glu Ieu Glu Lys Glu Ile Thr  
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**15** Lys Ile Gln Asn Phe Arg Val Tyr Tyr Asp Asp Ser Arg Asp Pro  
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 Ile Trp Lys Gly Pro Ala Lys Ieu Leu Trp Lys Gly Glu Gly Ala  
 1295 1300 1305  
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 Val Val Ile Glu Asp Asn Ser Asp Ile Lys Val Val Pro Arg Arg  
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**30**  
 Lys Ala Lys Ile Leu Arg Asp Tyr Gly Lys Gln Met Ala Gly Asp  
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 Asp Cys Val Ala Gly Arg Glu Asp Glu Asp Arg Ser Met Gly Gly  
 1340 1345 1350  
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 Lys Trp Ser Lys Gly Ser Ile Val Gly Trp Pro Gln Ile Arg Glu  
 1355 1360 1365  
 Arg Met Arg Arg Ala Phe Ala Ala Ala Pro Gly Val Gly Ala Val  
 1370 1375 1380  
**45**  
 Ser Gln Asp Leu Asp Lys His Gly Ala Ile Thr Ser Ser Asn Ile  
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 Asn Asn Pro Ser Cys Val Trp Leu Glu Ala Glu Glu Glu Glu Glu  
 1400 1405 1410  
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 Val Gly Phe Pro Val Arg Phe Gln Val Pro Ieu Arg Pro Met Thr  
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**60**  
 Tyr Lys Gly Ala Phe Asp Leu Ser His Phe Ieu Lys Glu Lys Gly  
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**65**  
 Gly Leu Asp Gly Leu Ile Tyr Ser Arg Lys Arg Gln Glu Ile Leu  
 1445 1450 1455  
 Asp Leu Trp Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln  
 1460 1465 1470  
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 Asn Tyr Thr Pro Gly Phe Gln Val Arg Tyr Pro Leu Thr Phe Gly  
 1475 1480 1485





	130	135	140	
8	Arg Glu Gly Met Lys Asn Cys Ser Phe Asn Met Thr Thr Glu Leu Arg 145	150	155	160
10	Asp Lys Lys Glu Glu Val Tyr Ser Leu Phe Tyr Arg Leu Asp Ile Glu 165	170	175	
	Lys Ile Asn Ser Ser Asn Asn Ser Glu Tyr Arg Leu Val Asn Cys 180	185	190	
15	Asn Thr Ser Ala Ile Thr Glu Ala Cys Pro Lys Val Thr Phe Glu Pro 195	200	205	
20	Ile Pro Ile His Tyr Cys Ala Pro Ala Glu Phe Ala Ile Leu Lys Cys 210	215	220	
25	Asn Asp Thr Glu Phe Asn Gly Thr Glu Pro Cys Lys Asn Val Ser Thr 225	230	235	240
	Val Glu Cys Thr His Glu Ile Lys Pro Val Val Ser Thr Glu Ieu Ieu 245	250	255	
30	Ieu Asn Glu Ser Leu Ala Glu Arg Glu Val Arg Ile Arg Ser Glu Asn 260	265	270	
35	Ile Ala Asn Asn His Lys Asn Ile Ile Val Glu Phe Ala Ser Pro Val 275	280	285	
40	Iys Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys Ser Tyr Arg 290	295	300	
45	Ile Glu Pro Glu Glu Thr Phe Tyr Ala Thr Asp Ile Val Glu Asp Ile 305	310	315	320
	Arg Glu Ala His Cys Asn Val Ser Arg Thr Asp Trp Asn Asn Thr Ile 325	330	335	
50	Arg Leu Val Ala Asn Glu Leu Arg Lys Tyr Phe Ser Asn Lys Thr Ile 340	345	350	
55	Ile Phe Thr Asn Ser Ser Gly Glu Asp Leu Glu Ile Thr Thr His Ser 355	360	365	
60	Phe Asn Cys Glu Gly Glu Phe Phe Tyr Cys Asn Thr Ser Glu Ieu Phe 370	375	380	
65	Asn Ser Thr Thr Thr Thr Asn Asn Met Glu Glu Ser Asn Asp Thr Ser 385	390	395	400
	Asn Glu Thr Ile Thr Leu Pro Cys Asn Ile Ieu Glu Ile Ile Asn Met			

408	418	425
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5      Trp Cys Arg Val Gly Cys Ala Met Tyr Ala Pro Pro Ile Glu Gly Val  
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10     Ile Arg Cys Glu Ser Asn Ile Thr Gly Leu Ile Ieu Thr Arg Asp Gly  
       435                          440                          445  
       Gly Asn Asn Ser Ala Asn Glu Thr Phe Arg Pro Gly Gly Asp  
       450                          455                          460

15     Ile Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Iys  
       465                          470                          475                          480

20     Ile Glu Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val Val  
       485                          490                          495

25     Glu Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val Phe Leu Gly Phe  
       500                          505                          510

30     Leu Gly Ala Ala Gly Ser Thr Met Gly Ala Ala Ser Ile Thr Leu Thr  
       515                          520                          525

35     Val Glu Ala Arg Cys Ile Leu Ser Gly Ile Val Glu Glu Glu Ser Asn  
       530                          535                          540

40     Leu Leu Arg Ala Ile Glu Ala Glu Glu Leu Leu Lys Leu Thr Val  
       545                          550                          555                          560

45     Trp Gly Ile Iys Glu Ile Glu Ala Arg Val Leu Ala Val Glu Arg Tyr  
       565                          570                          575

50     Leu Arg Asp Glu Glu Leu Leu Gly Ile Trp Gly Cys Ser Gly Lys Leu  
       580                          585                          590

55     Ile Cys Thr Thr Asn Val Pro Trp Asp Ser Ser Trp Ser Ser Lys Ser  
       600                          605                          610

60     Tyr Asp Asp Ile Trp Cys Asn Met Thr Trp Leu Glu Trp Asp Lys Glu  
       615                          620                          625

65     Ile Ser Asn Tyr Thr Asp Ile Ile Tyr Ser Leu Ile Glu Glu Ser Glu  
       635                          640                          645

70     Asn Glu Glu Glu Lys Asn Glu Glu Asp Leu Leu Ala Leu Asp Lys Trp  
       650                          655                          660

75     Ala Asn Leu Trp Asn Trp Phe Asp Ile Ser Lys Trp Leu Trp Tyr Ile  
       665                          670                          675

Arg Ser



Met Lys Val Iys Glu Thr Arg Iys Asn Tyr Gln His Ieu Trp Arg Trp  
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 Gly Thr Met Ieu Ieu Gly Met Ieu Met Ile Cys Ser Ala Ala Glu Gln  
 28 28 30  
**10**  
 Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Iys Glu Ala Thr  
 38 40 48  
**15**  
 Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val  
 58 58 60  
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 His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro  
 68 70 78 80  
**25**  
 Glu Glu Val Val Leu Gly Asn Val Thr Glu Tyr Phe Asn Asn Met Trp Iys  
 88 90 98  
**30**  
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 108 108 116  
**35**  
 Glu Ser Leu Iys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu  
 128 128 136  
**40**  
 Asp Cys Asp Asp Val Asn Thr Thr Asn Ser Thr Thr Thr Thr Ser Asn  
 148 148 148  
**45**  
 Gly Tyr Thr Gly Glu Ile Arg Lys Gly Glu Ile Lys Asn Cys Ser Phe  
 148 148 148 150  
 Asn Ile Thr Thr Ser Ile Arg Asp Iys Val Glu Lys Glu Tyr Ala Leu  
 168 170 178  
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 Phe Tyr Asn Leu Asp Val Val Pro Ile Asp Asp Asp Asn Ala Thr Thr  
 188 188 196  
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 Iys Asn Iys Thr Thr Arg Asn Phe Arg Leu Ile His Cys Asn Ser Ser  
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 218 218 226  
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 Thr Phe Asp Gly Lys Gly Ieu Cys Thr Asn Val Ser Thr Val Glu Cys  
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 Thr His Gly Ile Arg Pro Val Val Ser Thr Glu Ieu Ieu Leu Asn Gly  
 268 268 276

Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Met Asp  
 375 380 385

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 Asn Thr Lys Thr Ile Ile Val Glu Leu Asn Glu Ser Val Ala Ile Asn  
 390 395 396

**10**  
 Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Ile Gly Pro  
 398 400 402 403

**15**  
 Gly Arg Ala Phe Tyr Ala Ala Arg Lys Ile Ile Gly Asp Ile Arg Glu  
 408 410 412 413

Ala His Cys Asn Ile Ser Arg Ala Glu Trp Asn Asn Thr Leu Lys Glu  
 420 422 423

**20**  
 Ile Val Ile Lys Leu Arg Glu His Phe Gly Asn Lys Thr Ile Lys Phe  
 428 430 432 433

**25**  
 Asn Glu Ser Ser Gly Gly Asp Pro Glu Ile Val Arg His Ser Phe Asn  
 438 439 440

**30**  
 Cys Gly Gly Glu Phe Phe Tyr Cys Asp Thr Thr Glu Leu Phe Asn Ser  
 448 450 452 453

**35**  
 Thr Trp Asn Gly Thr Glu Gly Asn Asn Thr Glu Gly Asn Ser Thr Ile  
 468 470 472 473

Thr Leu Pro Cys Arg Ile Lys Glu Ile Asn Met Trp Glu Glu Val  
 480 482 484

**40**  
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Gly Gly Glu Ile Arg Cys Ser  
 490 492 494

**45**  
 Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Thr Glu Gly  
 500 502 504

**50**  
 Asn Gly Thr Glu Asn Glu Thr Glu Ile Phe Arg Pro Gly Gly Asp  
 518 520 522 524

**55**  
 Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys  
 535 536 538 540

Val Glu Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val Val  
**60** 548 550 552

Glu Arg

**65**  
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Ala Ala Gln Val Arg Val Ala Ala Ala Tyr Glu Thr Ala Tyr Gly  
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10

Ieu Thr Val Pro Pro Val Ile Ala Gln Asn Arg Ala Glu Leu Met  
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15

Ile Leu Ile Ala Thr Asn Ieu Ieu Gly Gln Asn Thr Pro Ala Ile Ala  
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20

Val Asn Gln Ala Glu Tyr Gly Glu Met Trp Ala Gln Asp Ala Ala Ala  
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25

Met Phe Gly Tyr Ala Ala Ala Thr Ala Thr Ala Thr Ala Thr Leu Leu  
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Pro Thr Glu Gln Ala Pro Glu Ser Thr Ser Ala Gly Gly Leu Leu Glu  
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Gln Ala Ala Ala Val Gln Gln Ala Ser Asp Thr Ala Ala Asn Gln  
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Leu Met Asn Asn Val Pro Gln Ala Leu Gln Gln Ieu Ala Gln Pro Thr  
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Gln Gly Thr Thr Pro Ser Ser Lys Ieu Gly Gly Leu Trp Lys Thr Val  
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Ser Pro His Arg Ser Pro Ile Ser Asn Met Val Ser Met Ala Asn Asn  
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His Met Ser Met Thr Asn Ser Gly Val Ser Met Thr Asn Thr Leu Ser  
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Ser Met Leu Lys Gly Phe Ala Pro Ala Ala Ala Gln Ala Val Gln  
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55

Thr Ala Ala His Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser  
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60

Ieu Gly Ser Ser Gly Lee Gly Gly Val Ala Ala Asn Leu Gly Arg  
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65

Ala Ala Ser Val Gly Ser Leu Ser Val Pro Gln Ala Trp Ala Asn Ala  
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Asn Gln Ala Val Thr Pro Ala Ala Arg Ala Leu Pro Leu Thr Ser Leu  
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**10** Arg Val Pro Pro Arg Pro Tyr Val Met Pro His Ser Pro Ala Ala Gly  
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 Ala Leu Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Gly Pro Gln  
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 Ile Gly Gly Gly Val Ala Val Gly Ile Pro Val Val Ala Met Gly Asn  
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84

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10 Leu Lys Gln Pro Ala Asp Gly Asn Pro Asp Pro Asn Ala Asn Pro Asn  
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15 Val Asp Pro Asn Ala Asn Pro Asn Val Asp Pro Asn Ala Asn Pro Asn  
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20 Val Asp Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn  
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25 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn  
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40 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn  
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45 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn  
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50 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn  
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55 Glu Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Lys Asn Asn Gln  
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60 Gly Asn Gly Gln Gly His Asn Met Asp Asn Asp Pro Asn Arg Asn Val  
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65 Asp Glu Asn Ala Asn Ala Asn Ser Ala Val Lys Asn Asn Asn Asn Glu  
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70 Glu Pro Ser Asp Lys His Ile Lys Glu Tyr Leu Asn Lys Ile Gln Asn  
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Ile Gln Val Arg Ile Lys Pro Gly Ser Ala Asn Lys Pro Lys Asp Glu

三

333 333 333

Leu Asp Tyr Ala Asn Asp Ile Glu Iys Iys Ile Cys Lys Met Glu Lys  
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60		atccatgt cccacccca tggaaatccc aatggaaaac ccaccccaaa ccggaaatggaa atccatgt cccacccca tggaaatccc aatggaaaac ccaccccaaa ccggaaatggaa	600

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10	Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala		
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25	Asn Asn Glu Glu Asn Gly Glu Lys Asn Met Trp Asn Asp Pro Asn		
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30	Arg Asn Val Asp Glu Asn Ala Asn Asn Ser Ala Val Lys Asn Asn		
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35	Ile Glu Asn Ser Leu Ser Thr Glu Trp Ser Pro Cys Ser Val Thr Cys		
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40	Gly Asn Gly Ile Glu Val Arg Ile Lys Pro Gly Ser Ala Asn Lys Pro		
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45	Ile Asp Glu Leu Asp Tyr Ala Asn Asp Ile Glu Lys Lys Ile Cys Lys		
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50	Leu Glu Pro Val Thr Asn Met Glu Asn Ile Thr Ser Gly Phe Ile Gly		
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55	Phe Leu Leu Val Leu Glu Asn Gly Phe Phe Leu Leu Thr Arg Ile Leu		
	75	80	85
60	Thr Ile Pro Glu Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu		
	85	90	95
65	Gly Gly Ser Pro Val Cys Leu Gly Glu Asn Ser Gln Ser Pro Thr Ser		
	90	95	100
70	Asn His Ser Pro Thr Ser Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp		
	95	100	105

Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys  
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6 Leu Ile Phe Leu Leu Val Ieu Ieu Asp Tyr Glu Gly Met Ieu Pro Val  
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10 Cys Pro Leu Ile Pro Gly Ser Thr Thr Thr Asn Thr Gly Pro Cys Lys  
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Tyr Cys Thr Thr Pro Ala Glu Gly Asn Ser Ser Val Pro Ser Cys Cys  
328 330 332

Cys Thr Iys Pro Thr Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser  
 349 355 356

Ser Trp Ala Phe Ala Tyr Tyr Leu Trp Glu Trp Ala Ser Val Arg Phe  
ser Tyr Glu  
~~ser~~ ~~Tyr~~ ~~Glu~~

25 Ser Thr Ieu Ser Ieu Ieu Val Pro Phe Val Gln Trip Phe Val Gly Ieu  
 323 324 325 326 327 328

30 Ser Pro Thr Val Trp Leu Ser Ala Ile Trp Met Ser Trp Tyr Trp Gly  
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35 Pro Ser Ieu Tyr Ser Ile Val Ser Pro Phe Ile Pro Leu Ieu Pro Ile  
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Phe Phe Cys Ile Thr Val Tyr Glu  
428

<2010> 20

~~403.1 x 343.2~~

For more information about the study, please contact Dr. Michael J. Koenig at (314) 747-2146 or via e-mail at [koenig@dfci.harvard.edu](mailto:koenig@dfci.harvard.edu).

$\times 800 \times 18$

<sup>50</sup> *Entomophagous insects as reservoirs of human diseases*, 1970.

*Scyphacidae* *Scyphacidae* *Scyphacidae* *Scyphacidae* *Scyphacidae*

60    *secaatccc* *caatccgggt* *ggggaggata* *tatcaggagggt* *ggatccatct* *ggggacca*

septostegite ectostegite mesostegite stactoglypta laevigata occasione

65        *eccteaggg actabgttgc ecgtatgtat sageccccbc yggcggggc ggtatccc*

scattered vegetations among which vegetation dominated by grasses.



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45	The Pro Glu Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln	56	64	73	82	91	100	
50	Ala Ala Met Gln Asn Ile Lys Lys Glu Thr Ile Asn Gln Glu Cys Ala Glu	62	70	78	86	94	102	
55	Tyr Asp Arg Val His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln	68	76	84	92	100	108	
60	Met Arg Glu Pro Arg Gly Ser Asp Ile Ala Gly Thr Ser Thr Leu	100	108	116	124	132	140	
	Gln Glu Glu Ile Gly Tyr Met Thr Asn Asn Pro Pro Ile Pro Val Gly	112	120	128	136	144	152	
65	Glu Ile Tyr Lys Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg	128	136	144	152	160	168	

Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Glu Gly Pro Lys Glu  
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 Ala Ala Thr Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly  
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 Pro Gly His Lys Ala Arg Val Leu His Met Gly Pro Ile Ser Pro Ile  
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Glu Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Glu  
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Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu  
 680 685 700

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 700 710 715 720

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70 Thr Glu Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly  
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75 Val Arg Tyr Pro Leu Thr Phe Gly Trp Cys Tyr Lys Leu Val Pro Val  
 930 935 940

80 Glu Pro Asp Lys Val Glu Glu Ala Asn Lys Gly Glu Asn Thr Ser Leu  
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93

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Leu Glu Trp Arg Phe Asp Ser Arg Leu Ala Sce His His Val His Arg  
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Glu Leu His Pro Glu Tyr Phe Lys Asn Cys Asp Pro Met Gly Ala Arg  
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Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Arg Trp Glu Lys Ile  
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Arg Leu Arg Pro Gly Gly Lys Lys Tyr Lys Leu Lys His Ile  
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Leu Leu Glu Thr Ser Glu Gly Cys Arg Glu Ile Leu Gly Glu Leu  
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Gln Arg Ser Leu Gln Thr Gly Ser Glu Glu Leu Arg Ser Leu Tyr  
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Lys Asp Thr Lys Glu Ala Leu Asp Lys Ile Glu Glu Glu Asn Ser  
 1100 1105 1110

50

Lys Ser Lys Lys Ala Gln Gln Ala Ala Ala Asp Thr Gly His  
 1115 1120 1125

55

55

All references referred to in this application, including patent and patent applications, are incorporated herein by reference to the fullest extent possible.

6

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

10

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and 15 without limitation, the following claims:

Claims

1. A method of raising an immune response against a pathogen which comprises administering (i) one or more first immunogenic polypeptides derived from said pathogen; (ii) 5 one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant; wherein the one or more first immunogenic polypeptides, the one or more adenoviral vectors and the adjuvant are administered concomitantly.
2. A method of raising an immune response against a pathogen which comprises 10 administering (i) one or more first immunogenic polypeptides derived from said pathogen co-formulated with an adjuvant; and (ii) one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; wherein one or more immunogenic polypeptides and adjuvant, and one or more adenoviral vectors are administered concomitantly.
3. A method of stimulating the production of pathogen-specific CD4+ and/or CD8+ T-cells 15 and/or antibodies in mammals which comprises administering to said mammal (i) one or more first immunogenic polypeptides derived from a pathogen; (ii) one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant; wherein the one or more first immunogenic polypeptides, the one or more adenoviral vectors and the adjuvant are administered concomitantly, for example by administering an immunologically effective amount 20 of an aforesaid composition.
4. A method of raising an immune response against a pathogen which consists of (a) administering (i) one or more first immunogenic polypeptides derived from said pathogen; (ii) 25 one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant; wherein the one or more immunogenic polypeptide, the one or more adenoviral vector and the adjuvant are administered concomitantly; and (b) optionally repeating the steps of (a).
5. A method of raising an immune response against a pathogen which comprises 30 administering (i) one or more first immunogenic polypeptides derived from said pathogen; (ii) one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant; wherein the one or more first immunogenic polypeptides, the one or more adenoviral vectors and the adjuvant are administered concomitantly; and wherein the method does not 35 involve administering any priming dose of immunogenic polypeptide or polynucleotide encoding immunogenic polypeptide.

6. A method according to any one of claims 1 to 5 wherein one or more immunogenic polypeptides, one or more adenoviral vectors and an adjuvant are co-formulated.

7. A method according to any one of claims 1 to 6 wherein production of pathogen specific CD4+ T-cells and CD8+ T-cells and antibodies is stimulated.

5 8. A vaccine composition comprising (i) one or more first immunogenic polypeptides derived from a pathogen; (ii) one or more adenoviral vectors comprising one or more heterologous polynucleotide encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant.

9. A method or vaccine composition according to any one of claims 1 to 8 wherein one or 10 more of said one or more first immunogenic polypeptides is substantially the same as one or more of said one or more second immunogenic polypeptides.

10. A method or vaccine composition according to any one of claims 1 to 8 wherein one or more of said one or more first immunogenic polypeptides contains at least one antigen which is substantially the same as an antigen contained in one or more of said one or more second 15 immunogenic polypeptides.

11. A method or vaccine composition according to any one of claims 1 to 10 wherein one or more the first immunogenic polypeptides comprises at least one T cell epitope.

12. A method or vaccine composition according to any one of claims 1 to 11 wherein the one or more first immunogenic polypeptide comprises at least one B cell epitope.

20 13. A method or vaccine composition according to any one of claims 1 to 12 wherein one or more of said one or more first immunogenic polypeptides and one or more of said one or more second immunogenic polypeptides share one or more identical B-cell and/or T-cell epitopes.

14. A method or vaccine composition according to any one of claims 1 to 8 wherein none of the one or more of said one or more first immunogenic polypeptides is substantially the same as 25 or contains any antigen in common with one or more of said one or more second immunogenic polypeptides.

15. A method or vaccine composition according to any one of claims 1 to 14 wherein one or more of the adenoviral vectors is derived from a human adenovirus.

30 16. A method or vaccine composition according to claim 15 wherein the human adenovirus serotype is selected from Ad1, Ad2, Ad4, Ad5, Ad6, Ad11, Ad 24, Ad34 and Ad35.

17. A method or vaccine composition according to any one of claims 1 to 14 wherein one or more of the adenoviral vectors is derived from a non-human primate adenovirus.

35 18. A method or vaccine composition according to claim 17 wherein the non-human primate adenovirus serotype is selected from chimpanzee adenovirus serotypes Pan5, Pan8, Pan7 and Pan9.

19. A method or vaccine composition according to any one of claims 1 to 18 wherein the pathogen is HIV.

20. A method or vaccine composition according to claim 19 wherein the immunogenic polypeptides contain HIV derived antigens which are selected from Env, Nef, Gag, and Pol and immunogenic derivatives thereof and immunogenic fragments thereof.
21. A method or vaccine composition according to claim 20 wherein a first immunogenic polypeptide is p24-RT-Nef-p17.
22. A method or vaccine composition according to claim 20 or claim 21 wherein a second immunogenic polypeptide is Gag-RT-Nef.
23. A method or vaccine composition according to any one of claims 1 to 18 wherein the pathogen is *Plasmodium falciparum* and/or *Plasmodium vivax*.
- 10 24. A method or vaccine composition according to claim 23 wherein the immunogenic polypeptides contain antigens derived from *Plasmodium falciparum* and/or *Plasmodium vivax* which are selected from circumsporozoite (CS) protein, MSP-1, MSP-3, AMA-1, LSA-1, LSA-3 and immunogenic derivatives thereof or immunogenic fragments thereof.
- 15 25. A method or vaccine composition according to claim 24 wherein a/the immunogenic polypeptide is the hybrid protein RTS.
26. A method or vaccine composition according to claim 25 wherein RTS is presented in the form of a mixed particle known as RTS,S.
- 20 27. A method or vaccine composition according to any one of claims 24 to 26 wherein a/the immunogenic polypeptide encoded by a polynucleotide is the CS protein from *Plasmodium falciparum* or immunogenic fragment thereof.
28. A method or vaccine composition according to any one of claims 1 to 18 wherein the pathogen is *Mycobacterium tuberculosis*.
29. A method or vaccine composition according to any one of claims 1 to 28 wherein the adjuvant comprises a preferential stimulator of Th1 responses.
- 25 30. A method or vaccine composition according to claim 29 wherein the adjuvant comprises QS21 and/or 3D-MPL and/or CpG.
31. A method or vaccine composition according to claim 30 wherein the adjuvant comprises QS21 and 3D-MPL.
32. A method or vaccine composition according to any one of claims 1 to 31 wherein the adjuvant contains an oil-in-water emulsion.
33. A method or vaccine composition according to any one of claims 1 to 31 wherein the adjuvant contains liposomes.
34. A method of stimulating an immune response in a mammal which comprises administering to a subject an immunologically effective amount of a vaccine composition according to any one of claims 8 to 33.
- 35 35. Use of a vaccine composition according to any one of claim 8 to 33 in the manufacture of a medicament for stimulating an immune response in a mammal.

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36. A vaccine composition according to any one of claims 8 to 33 for use in stimulating an immune response in a mammal.

37. A kit comprising (i) one or more first immunogenic polypeptides derived from a pathogen; (ii) one or more adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more second immunogenic polypeptides derived from said pathogen; and (iii) an adjuvant.

38. A kit comprising (i) one or more first immunogenic polypeptides derived from a pathogen and an adjuvant; and (ii) one or more second adenoviral vectors comprising one or more heterologous polynucleotides encoding one or more immunogenic polypeptides derived from said pathogen.

39. A method, or vaccine, or kit, or use according to any preceding claim wherein the first immunogenic polypeptide comprises p24-RT-Nef-p17, the adjuvant comprises 3D-MPL and QS21 in a liposome such as adjuvant B-heskin, and the adenoviral vector comprises a chimpanzee adenovirus serotype Pan7 vector comprising a polynucleotide encoding the immunogenic polypeptide Gag-RT-Nef, optionally codon optimised.

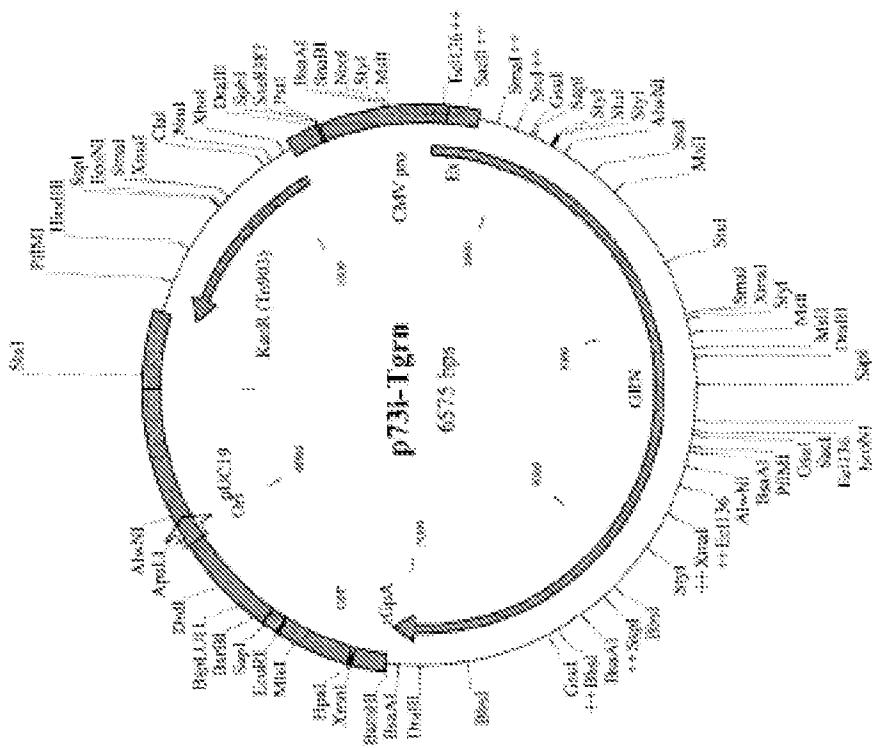
40. A method, or vaccine, or kit, or use according to any preceding claim wherein one, or two, or all of the polypeptide, adenoviral vector and adjuvant components are combined with a pharmaceutically acceptable excipient.

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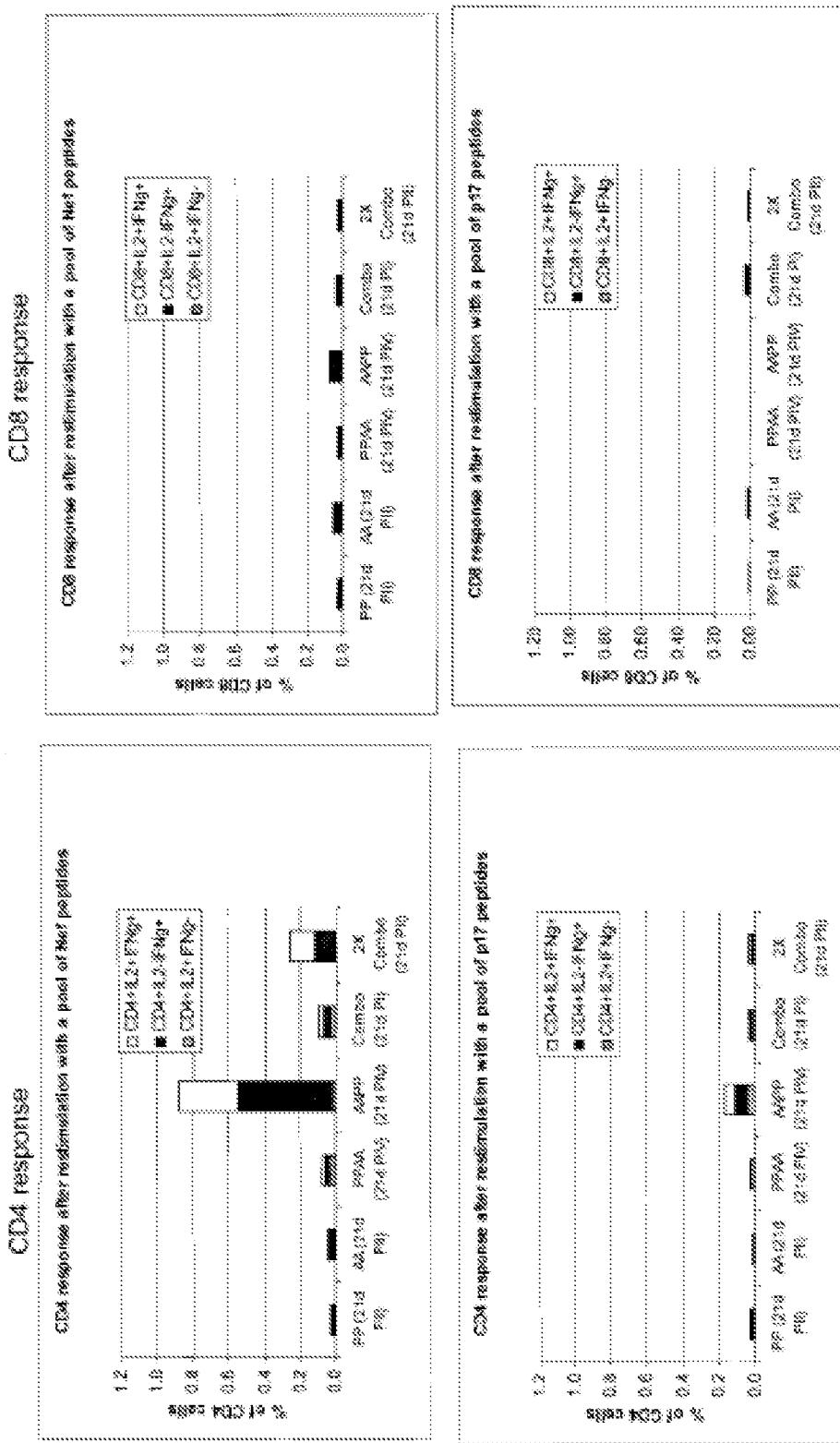
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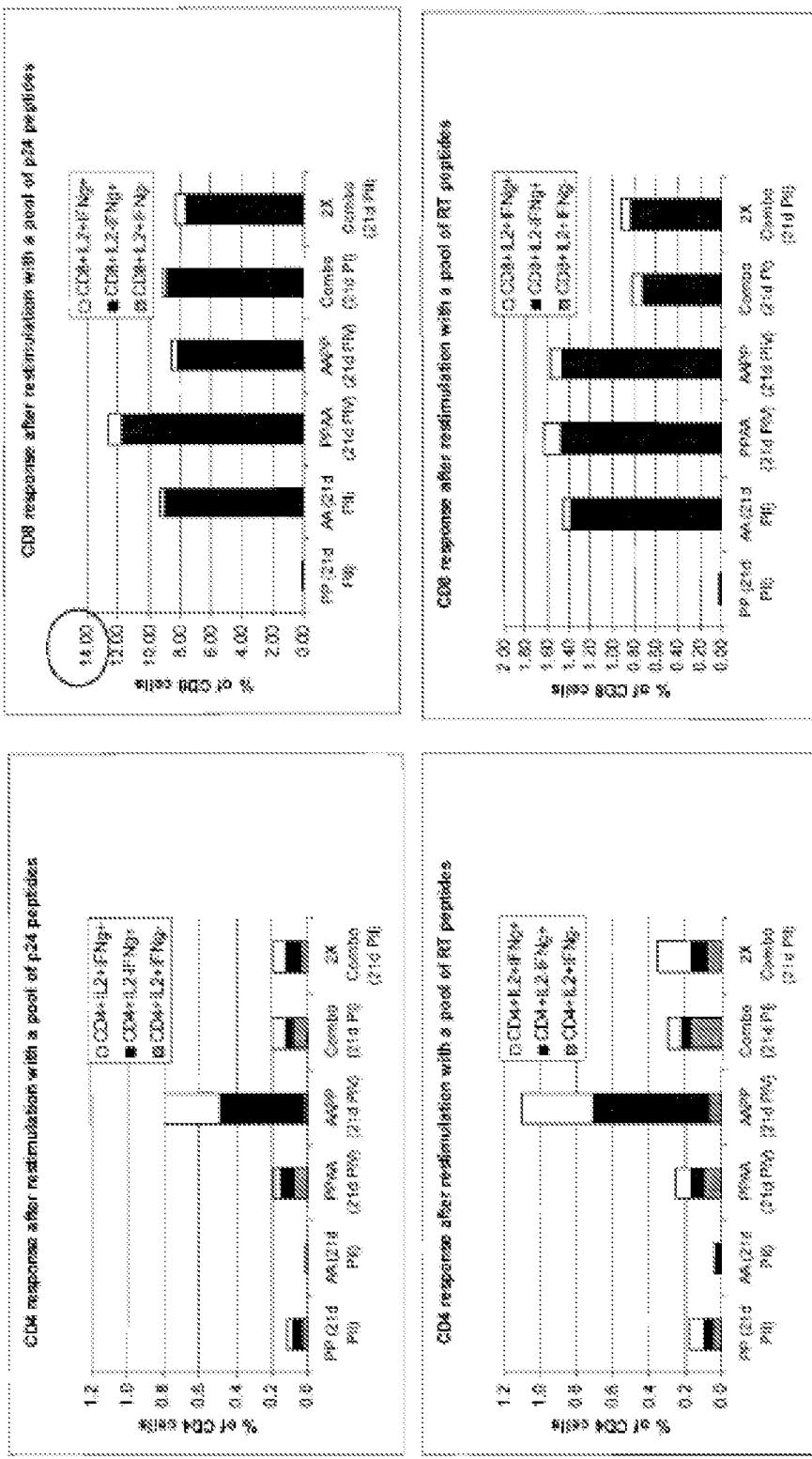


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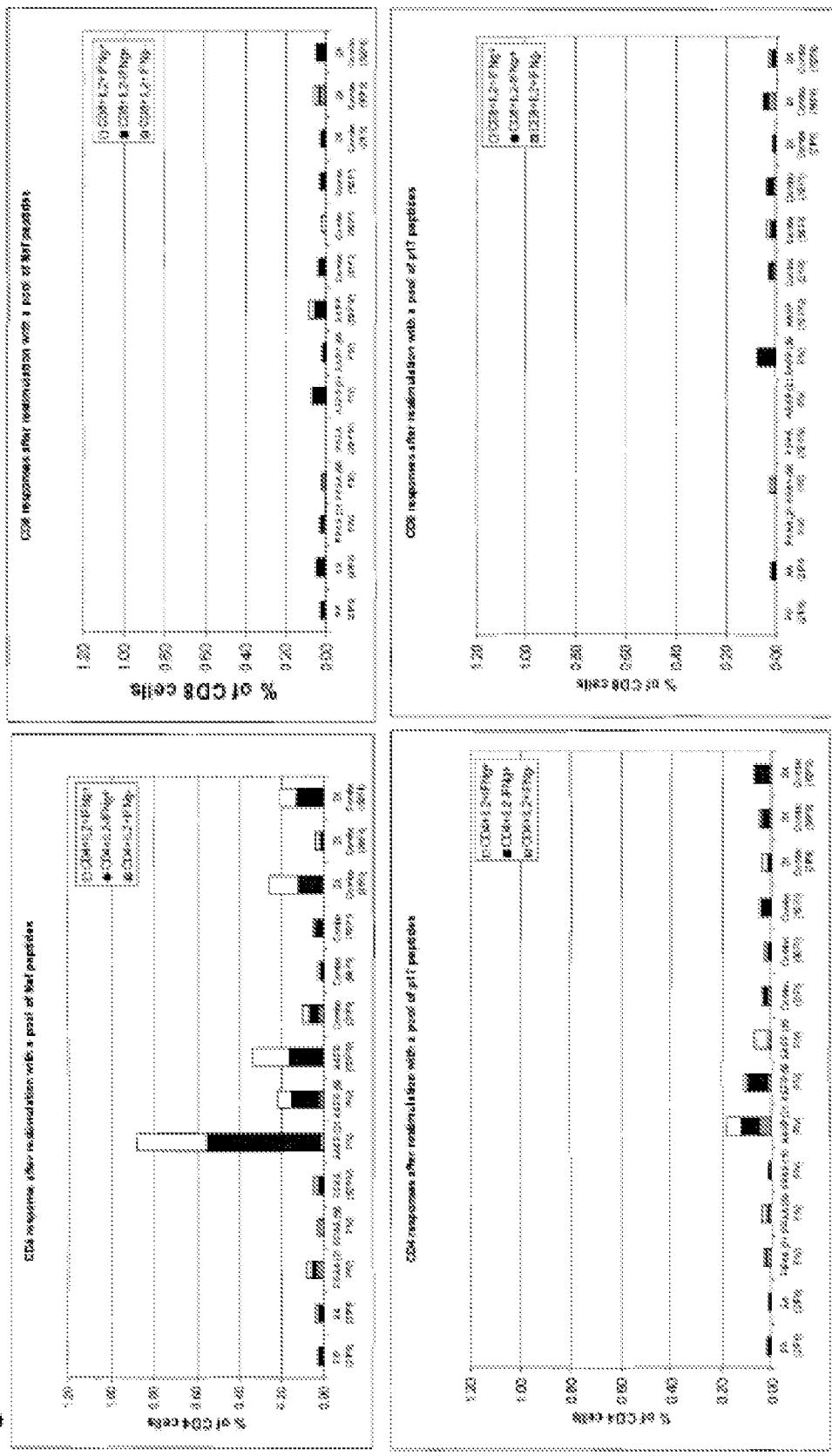
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Figure 2b CD4 response



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Figure 3



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Figure 3b

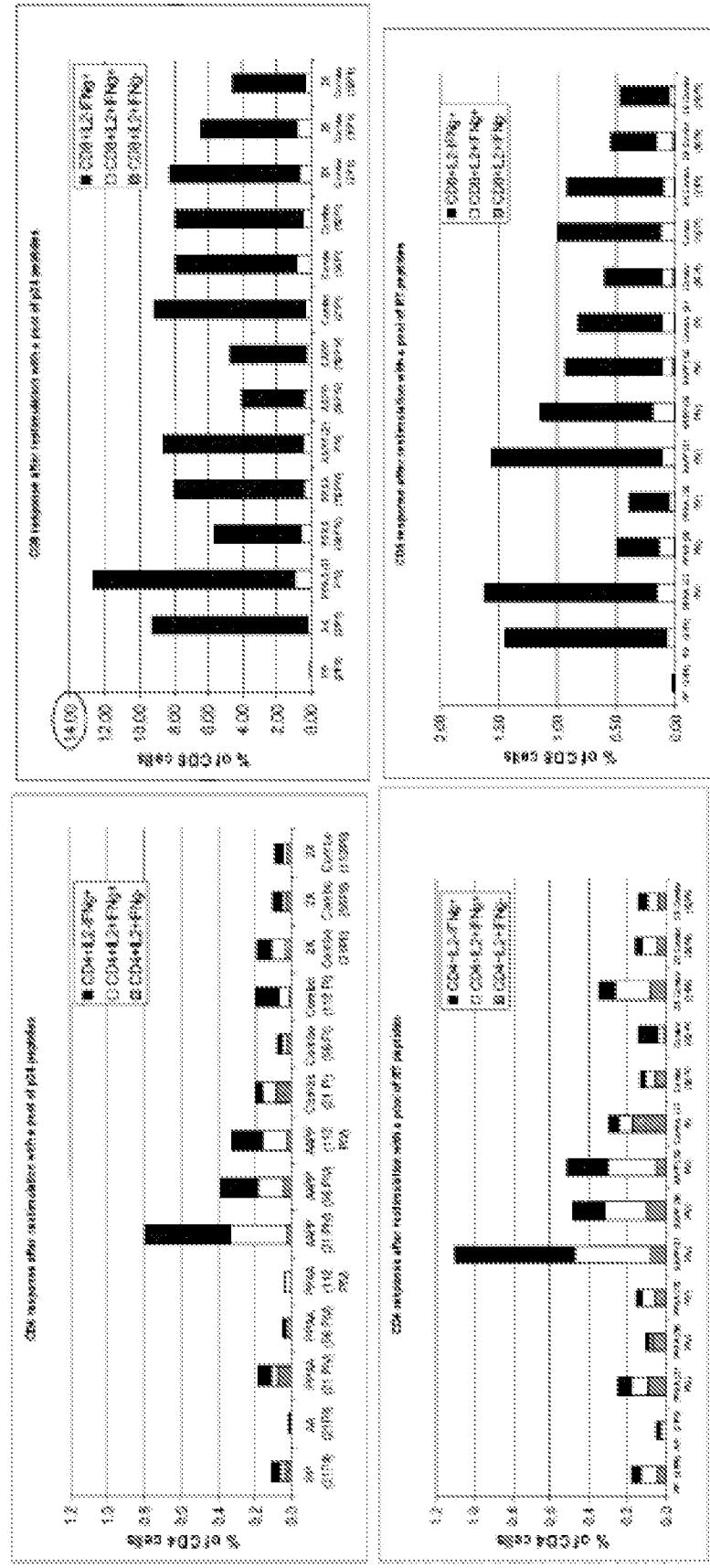
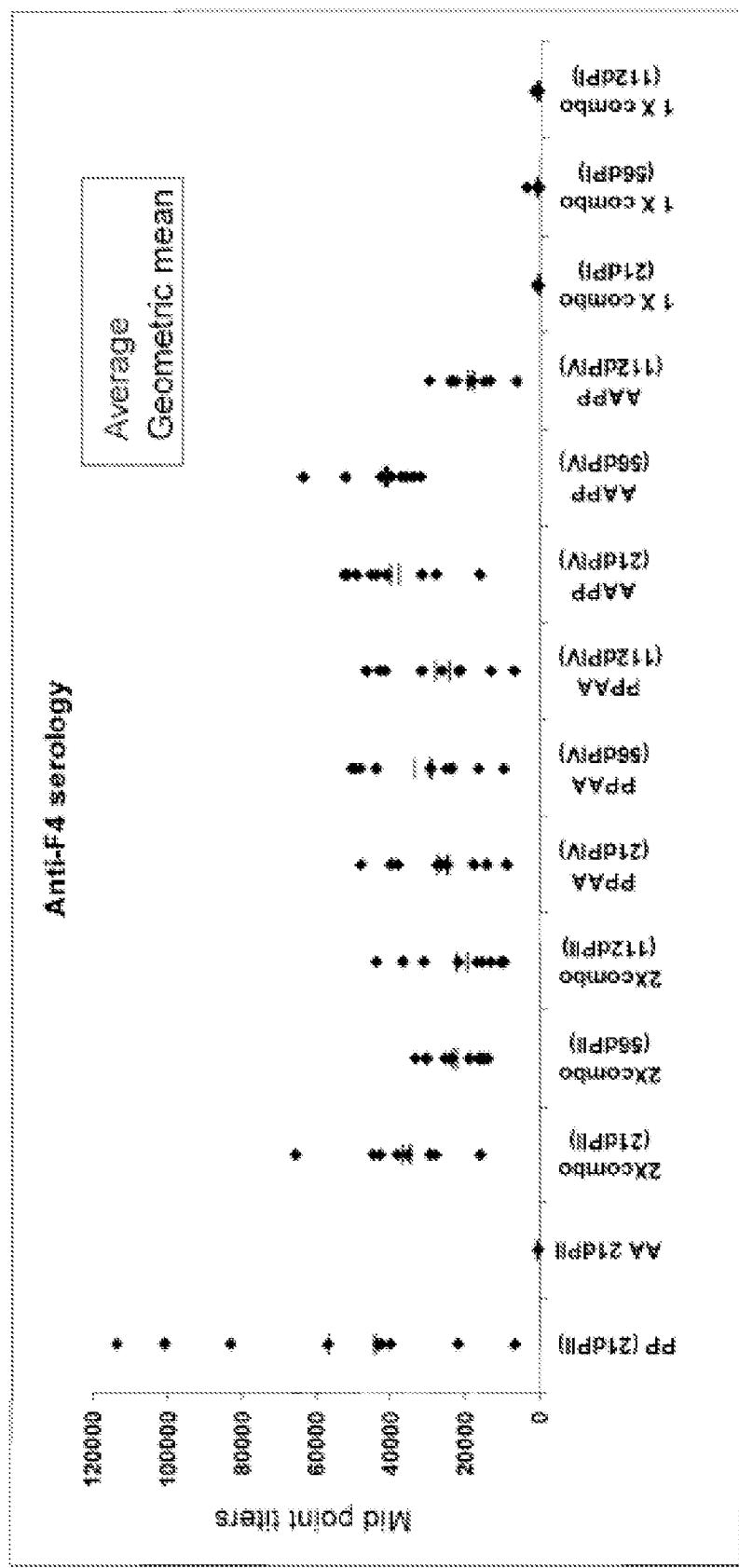




Figure 4



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Figure 5

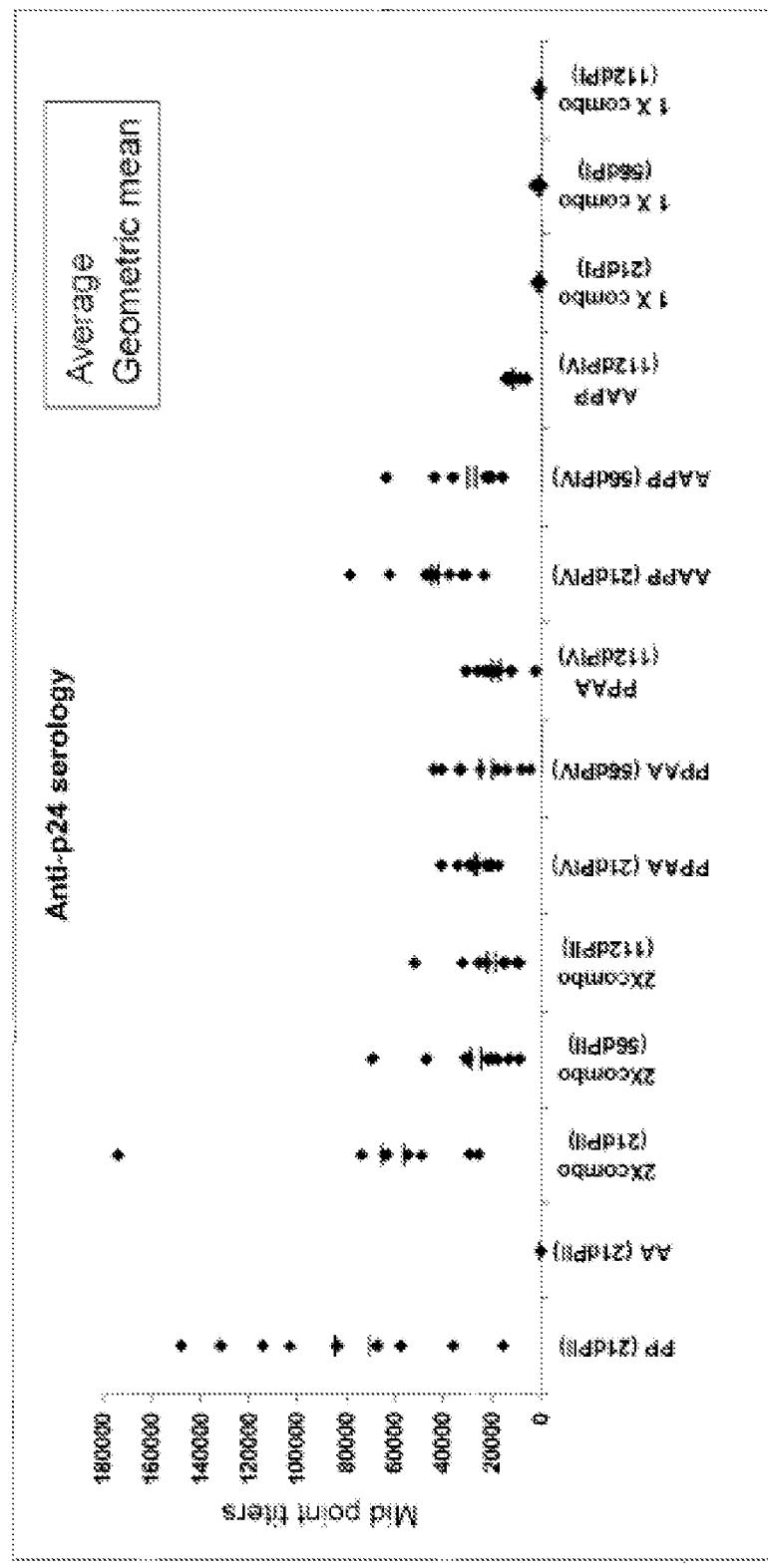
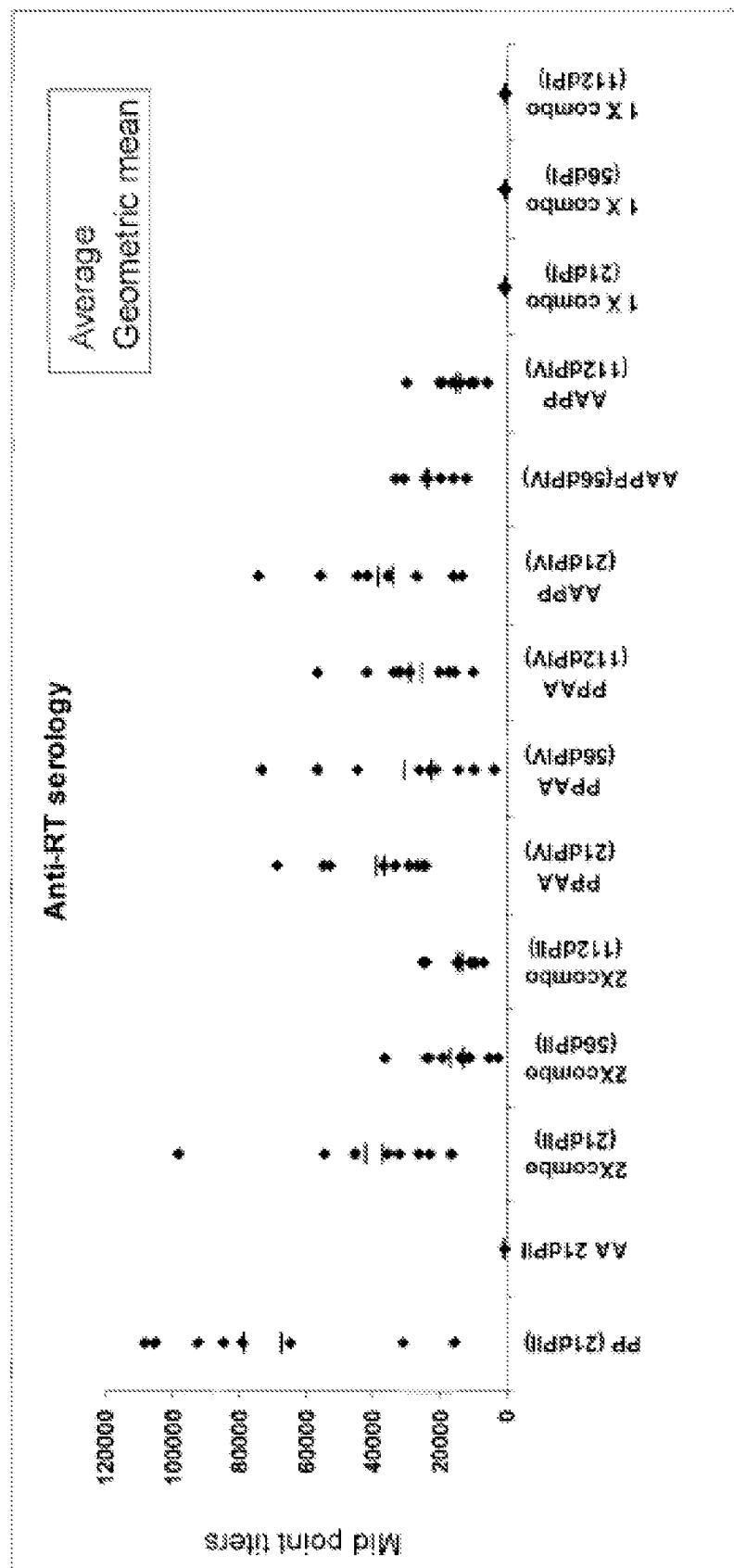


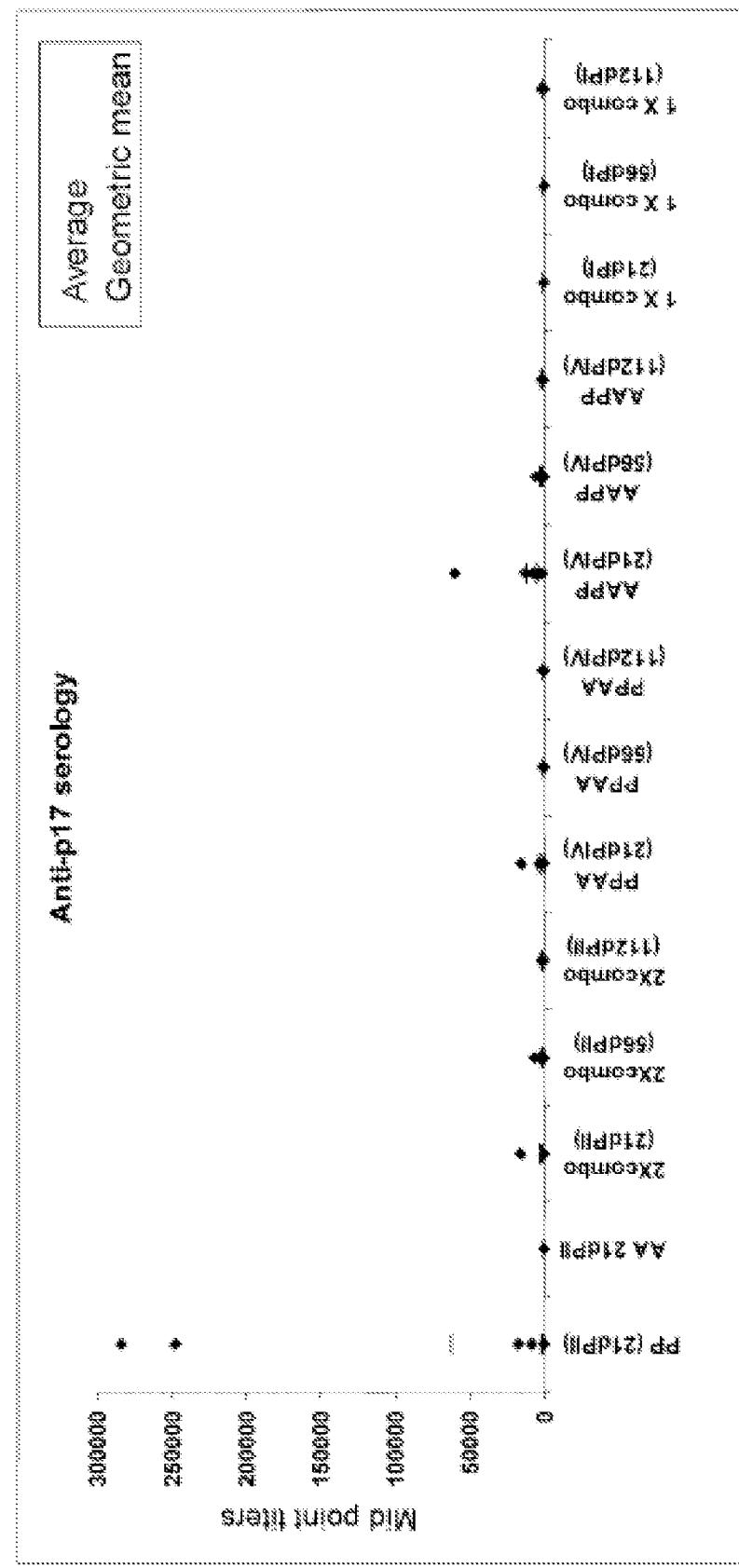


Figure 6



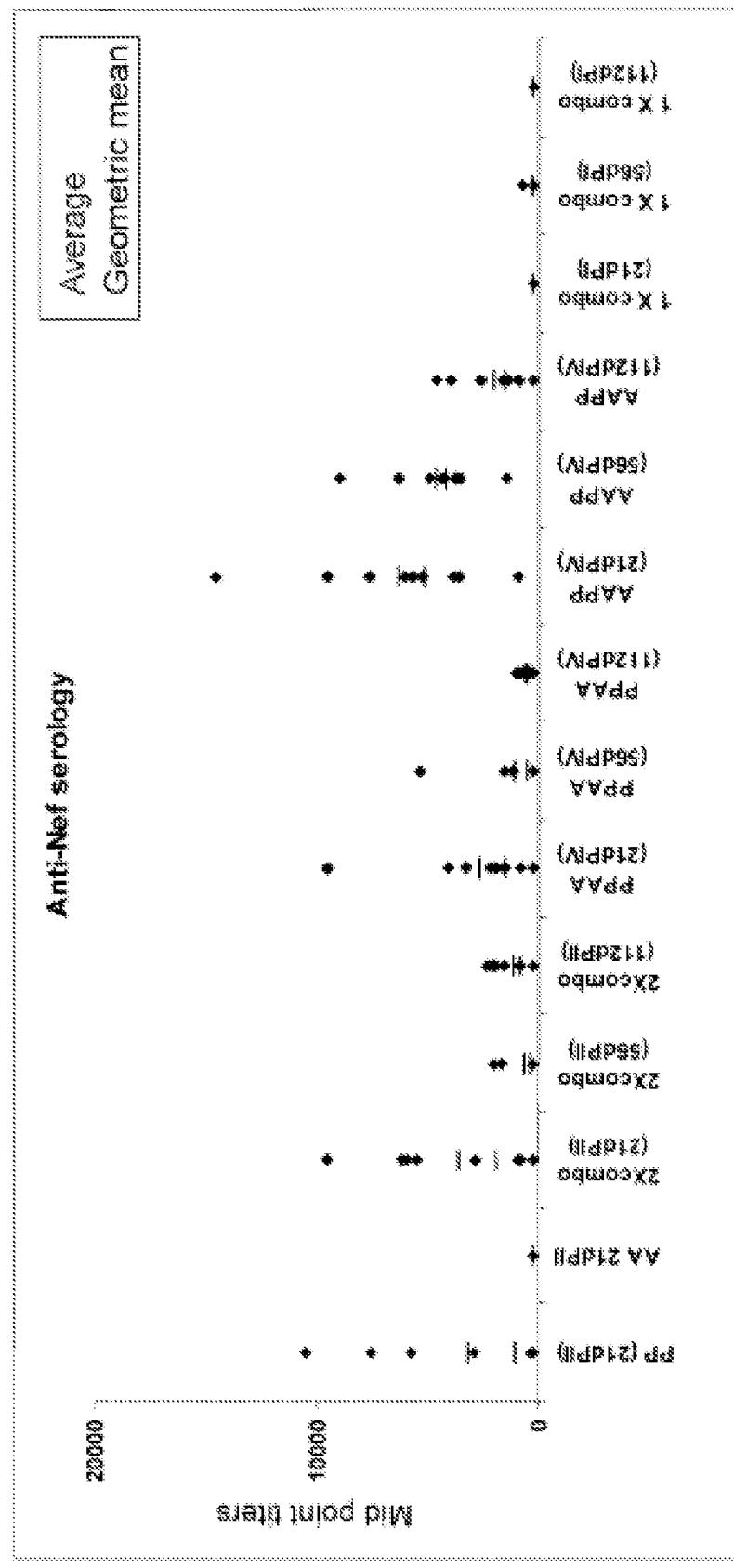
9/27

Figure 7



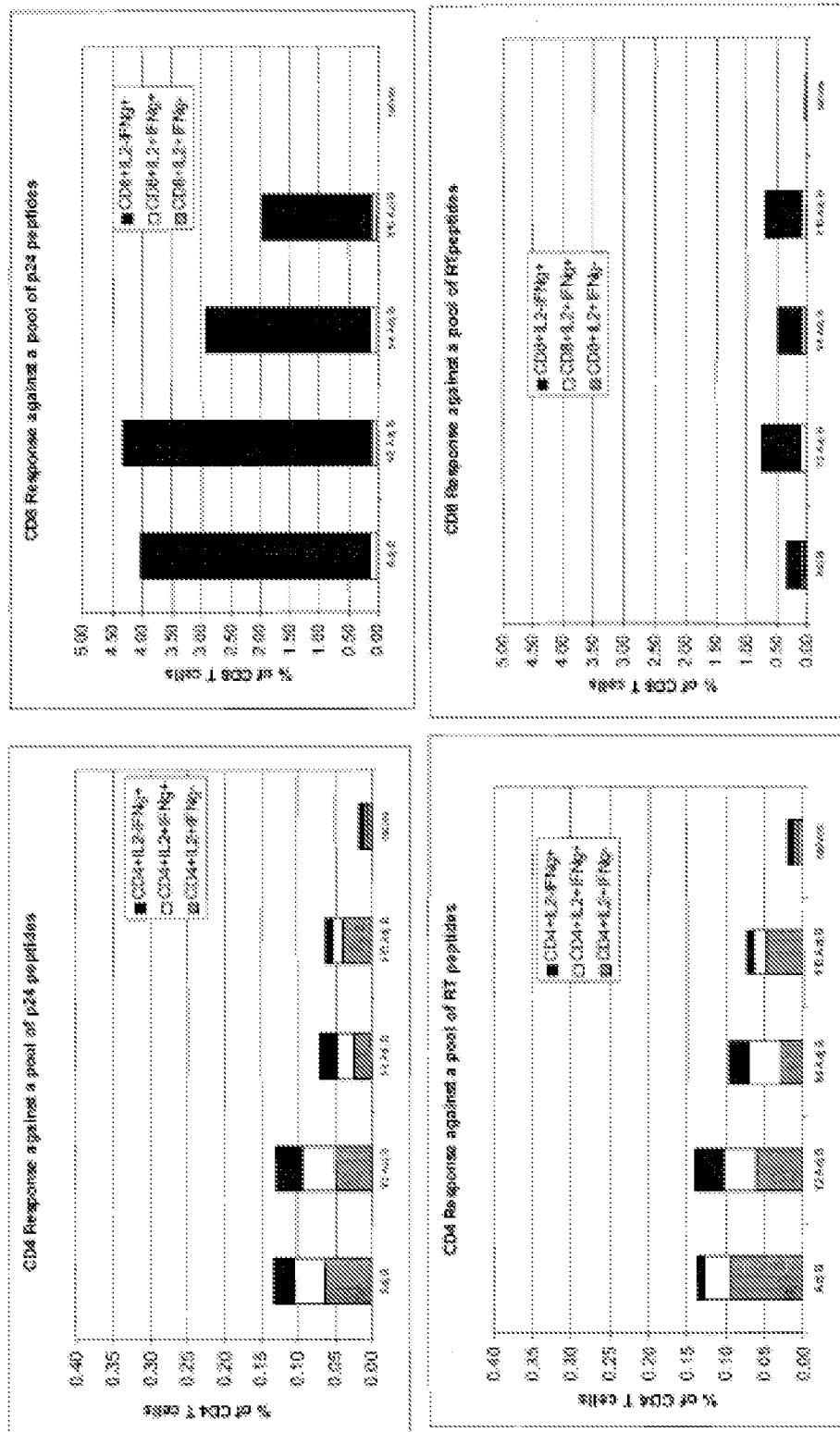
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Figure 8



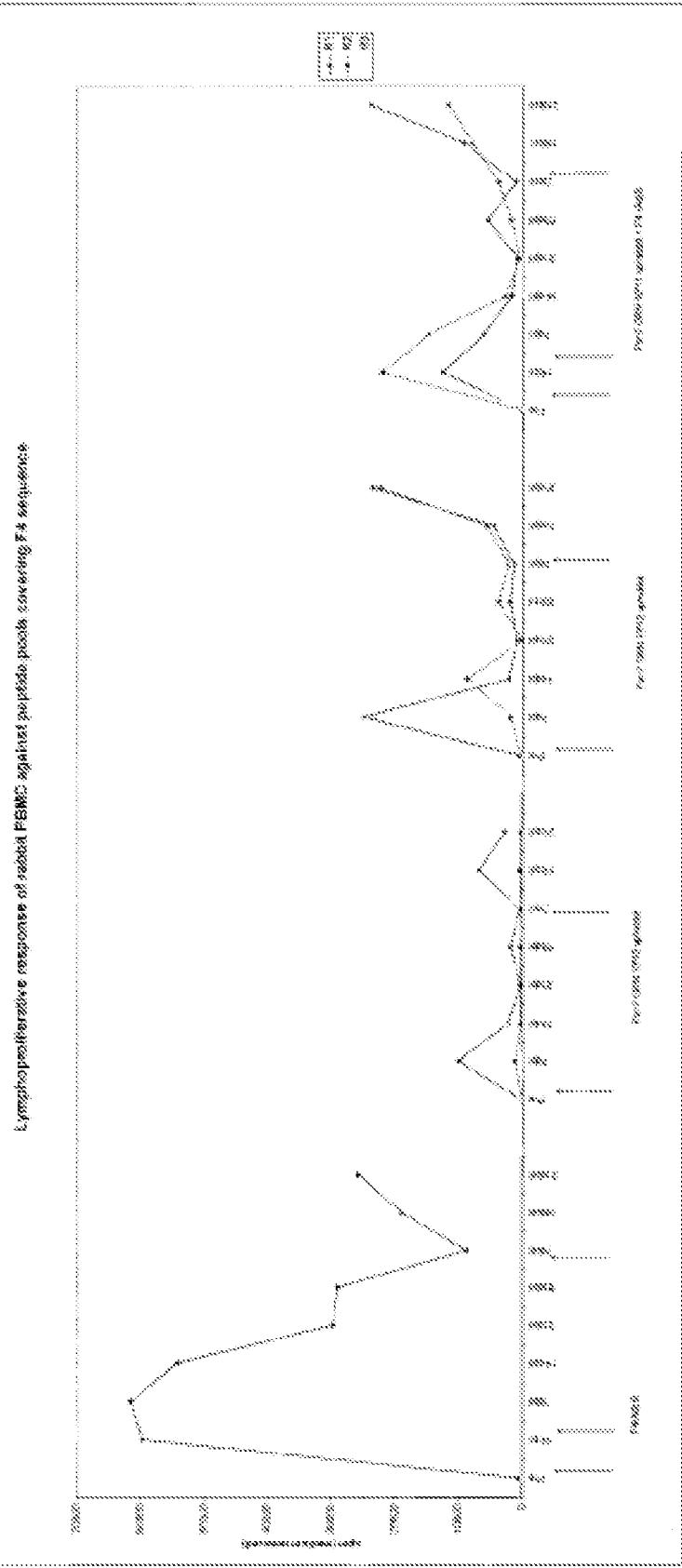
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Figure 9

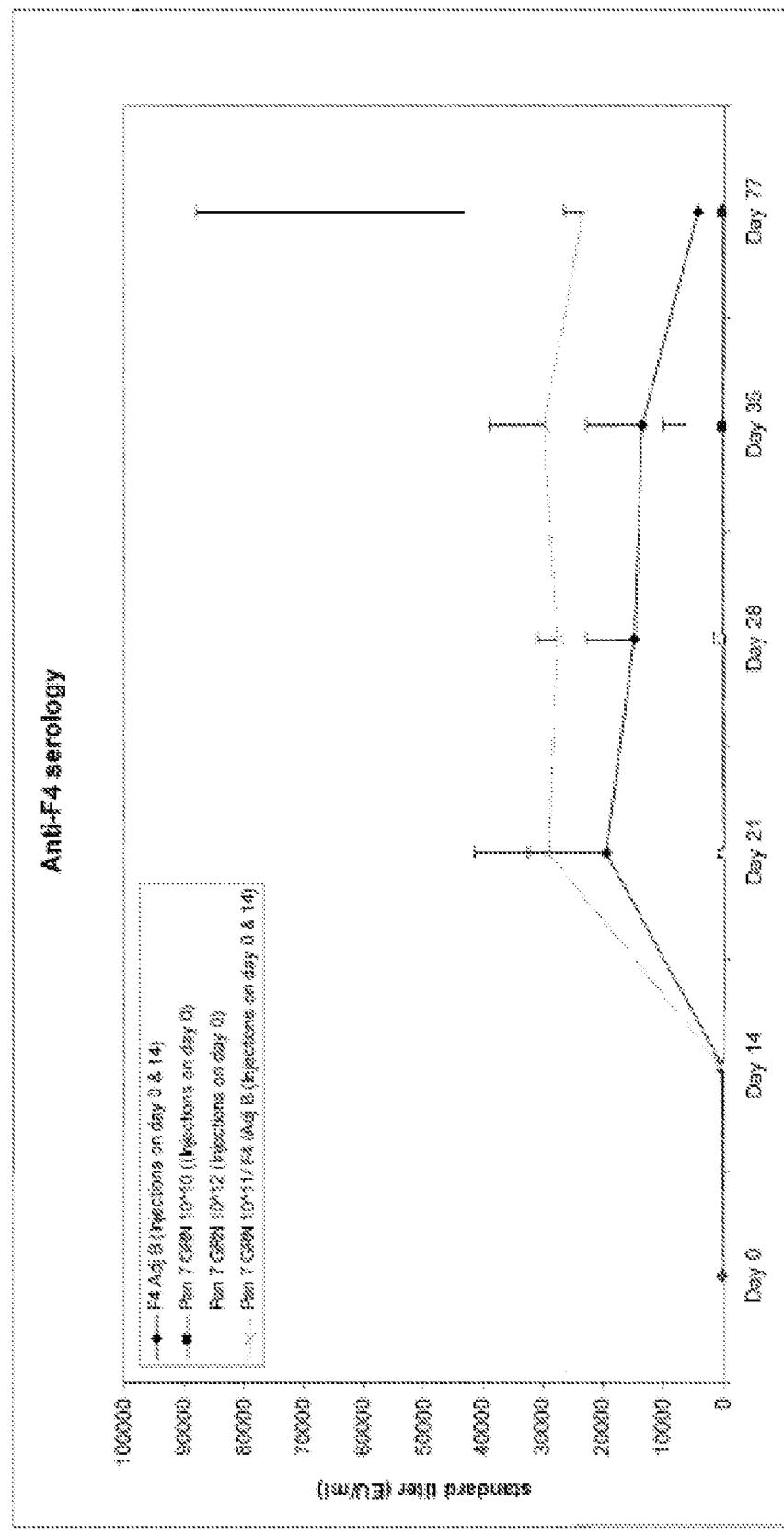


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Figure 10

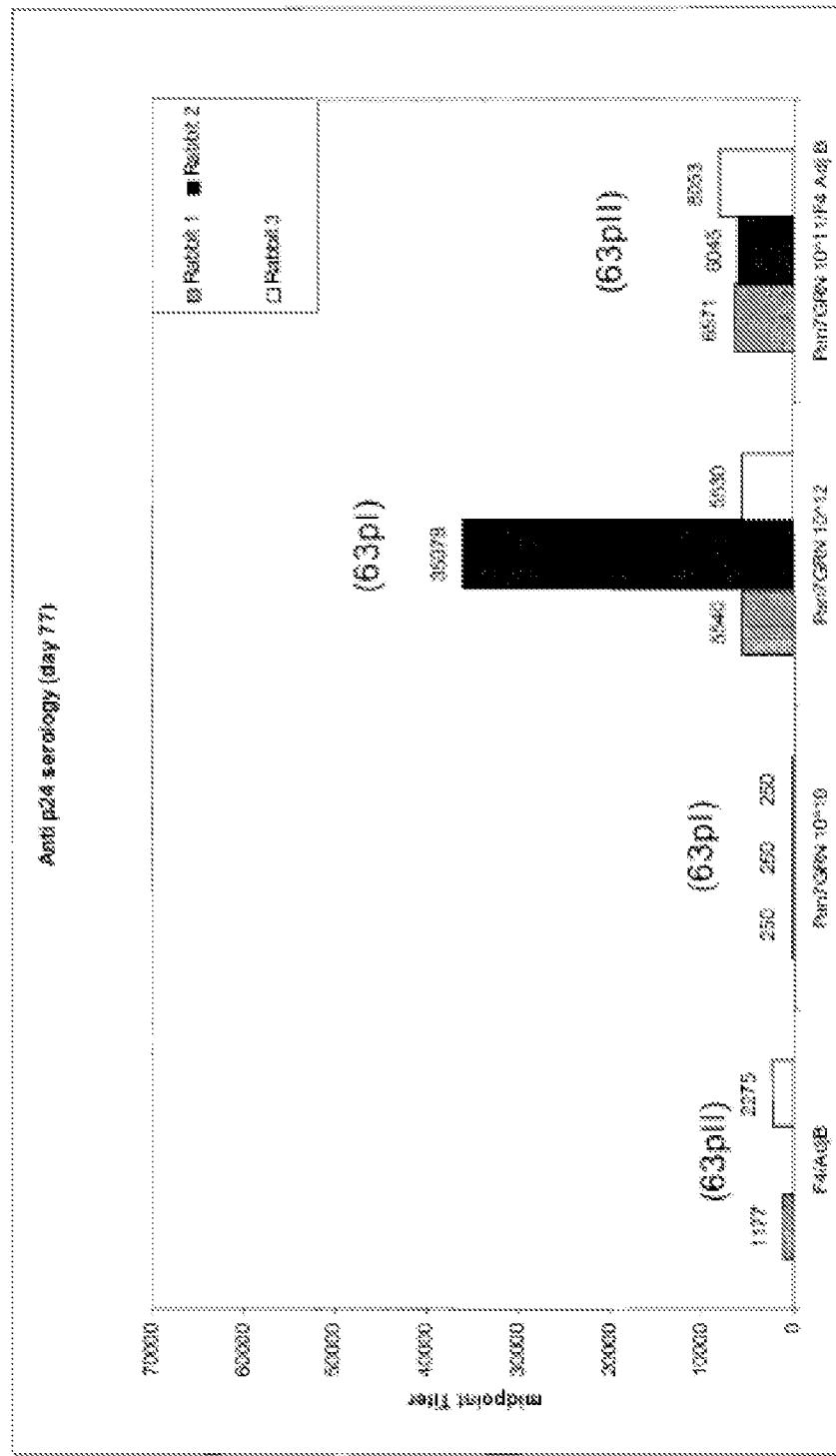


**Figure 14**  
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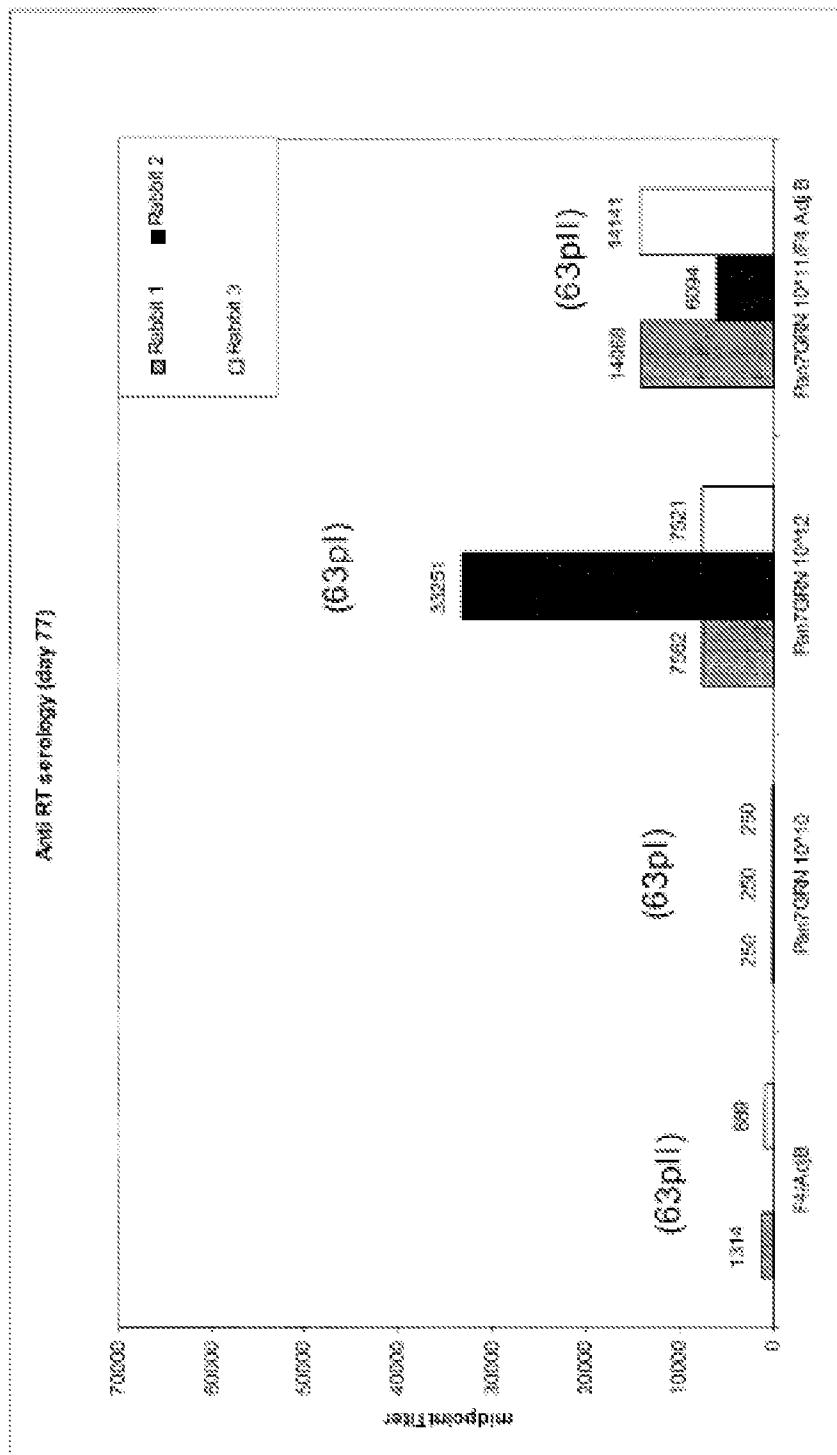
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Figure 12a



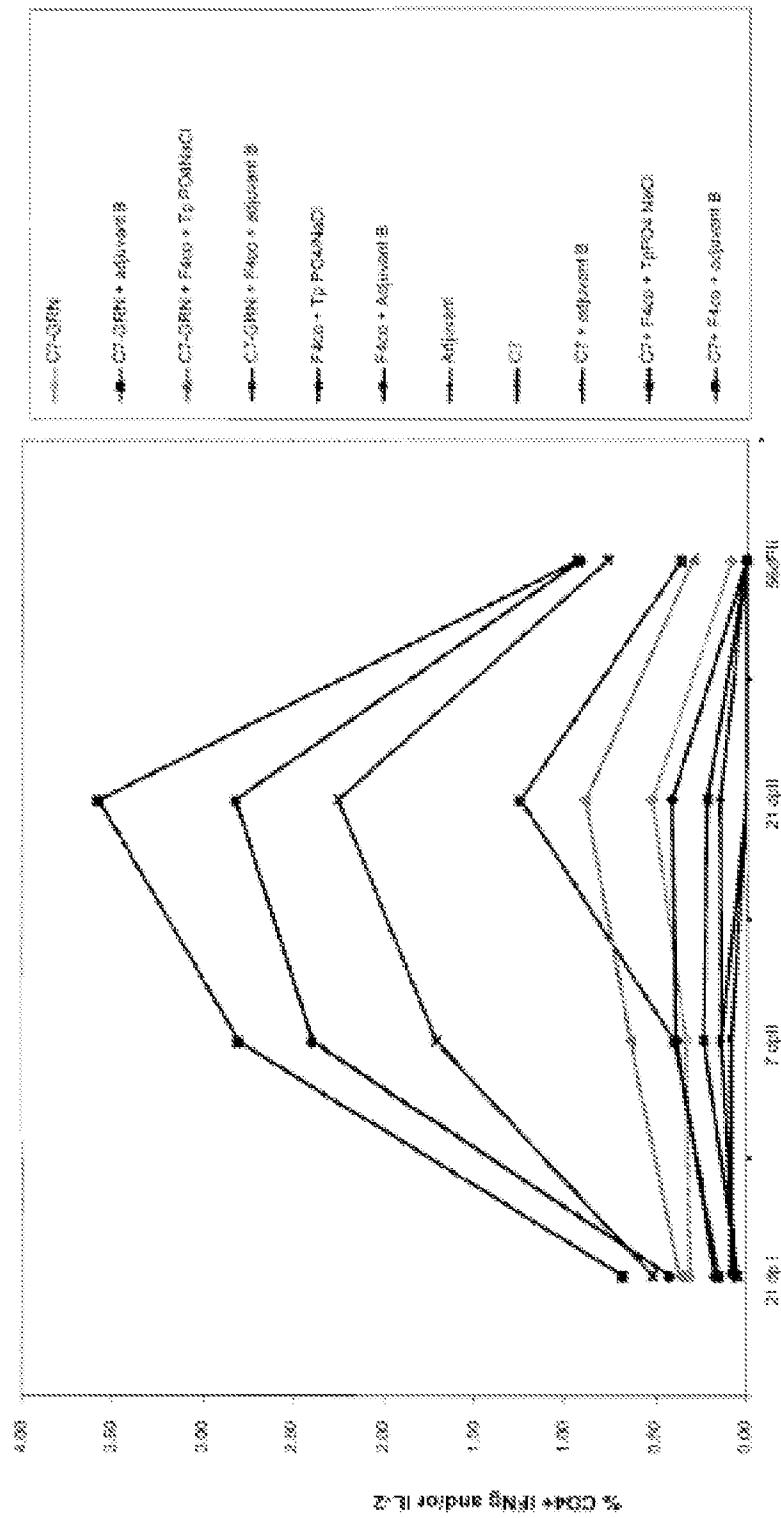
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**Figure 12b**

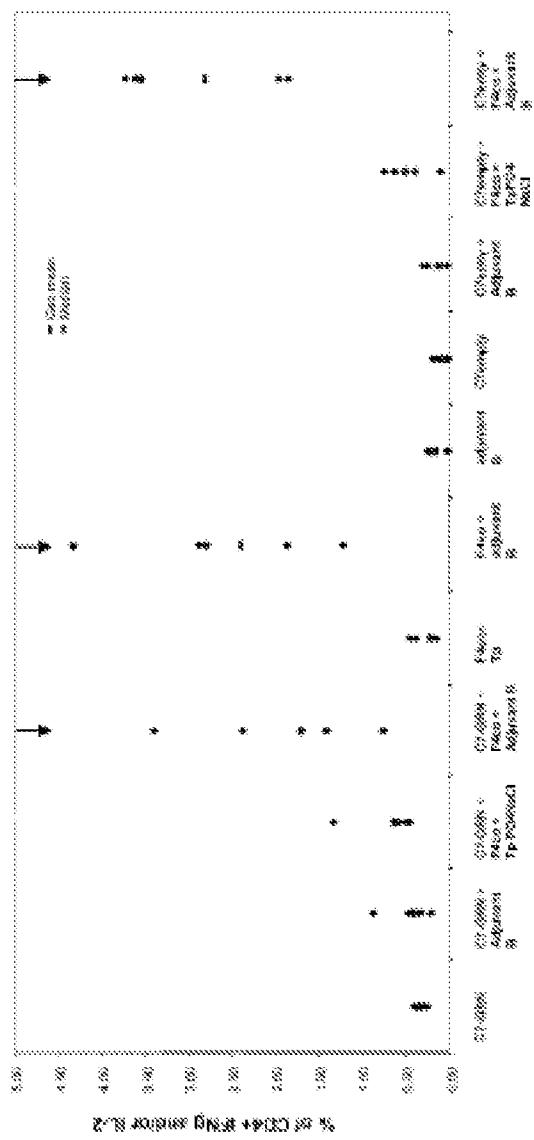




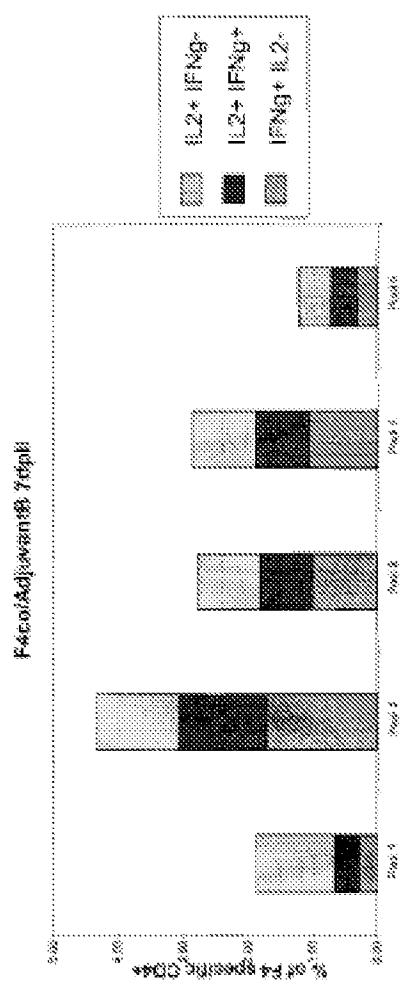
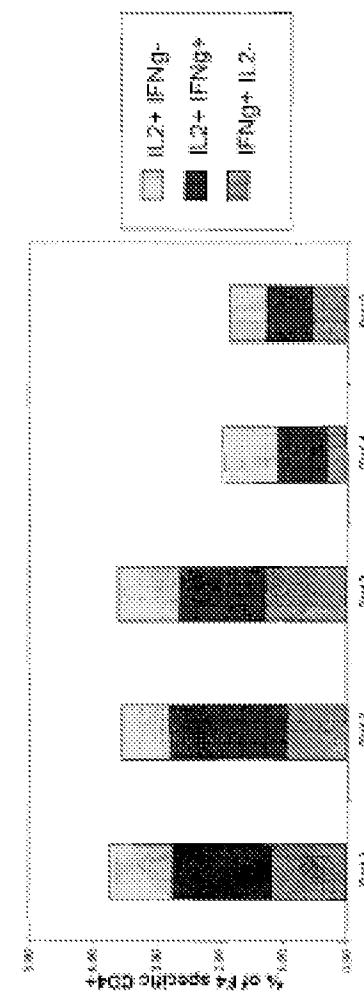
**Figure 13**



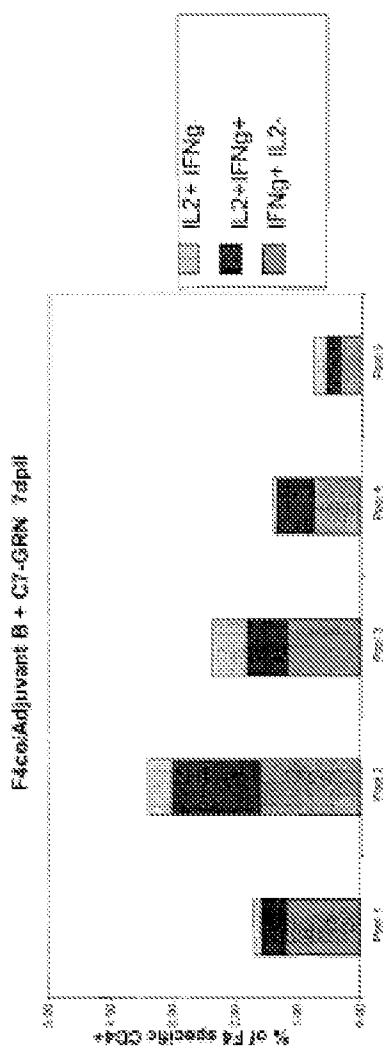
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**Figure 14**

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**Figure 15A****Figure 15B**

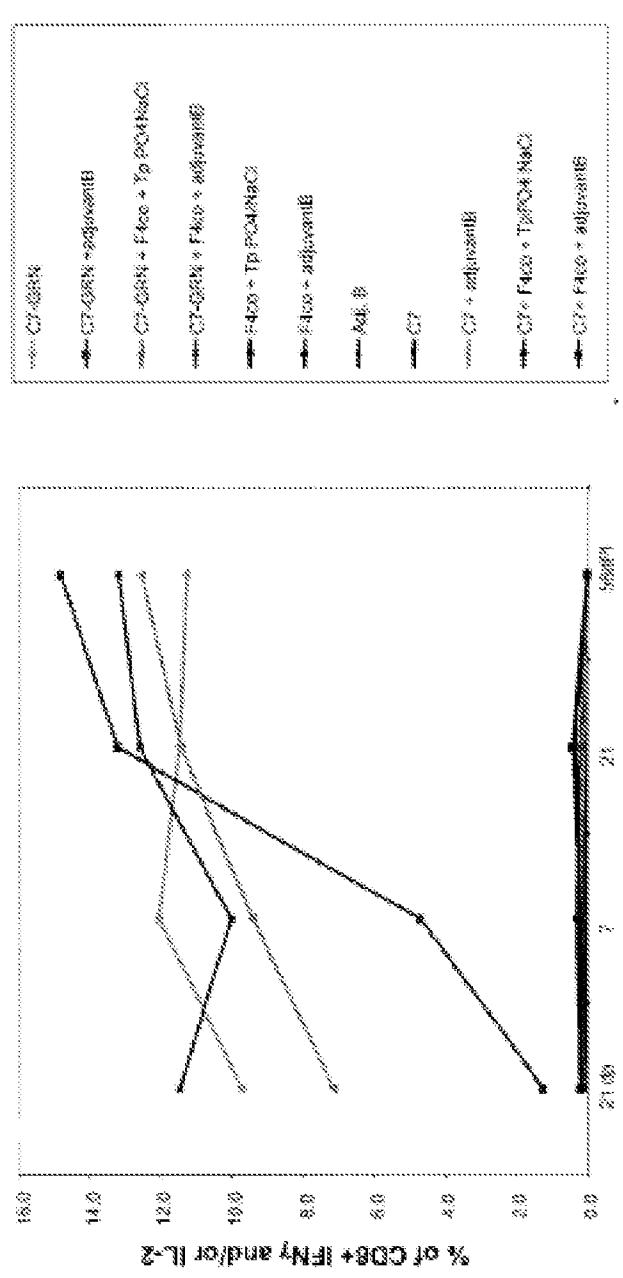
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**Figure 15C**

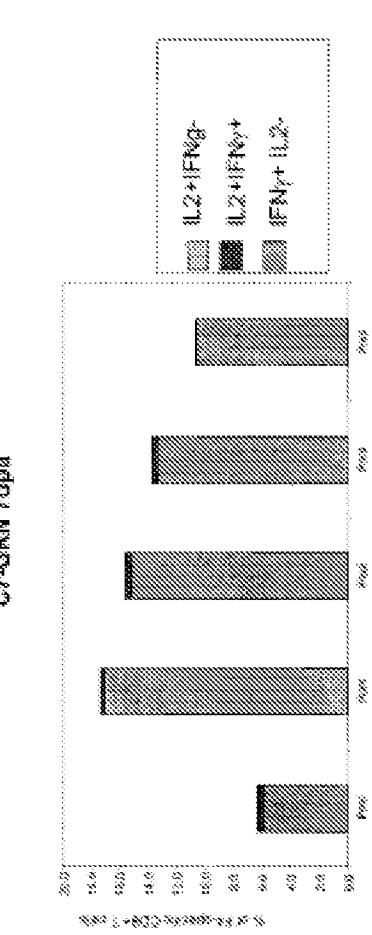
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Figure 16



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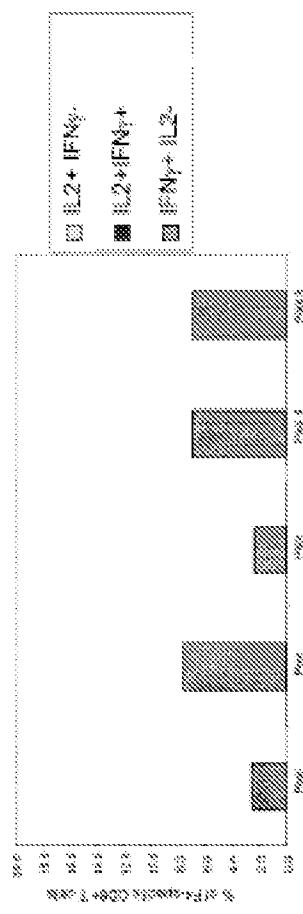
Figure 17A



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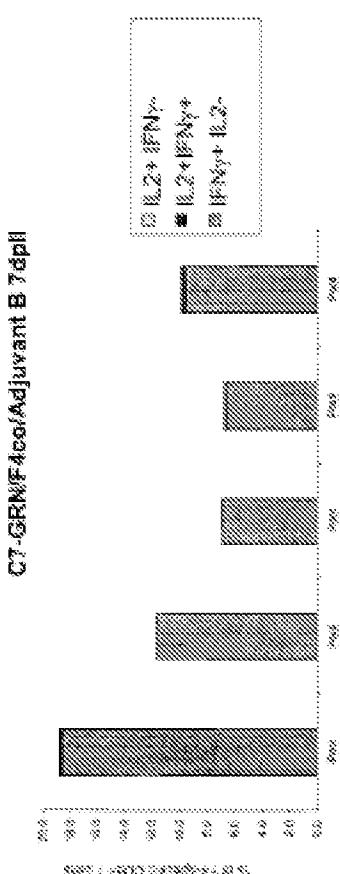
Figure 17B

## C7-GRN Adjacent to TepII



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Figure 4



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Figure 18

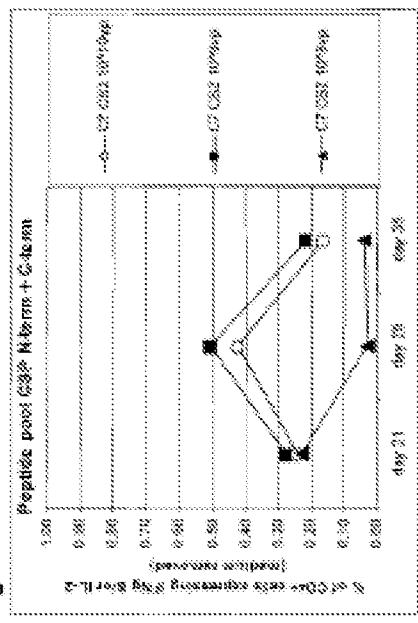
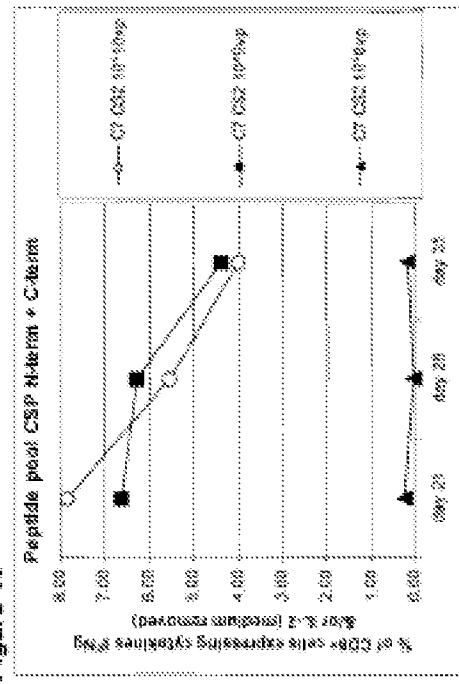


Figure 19



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Figure 20

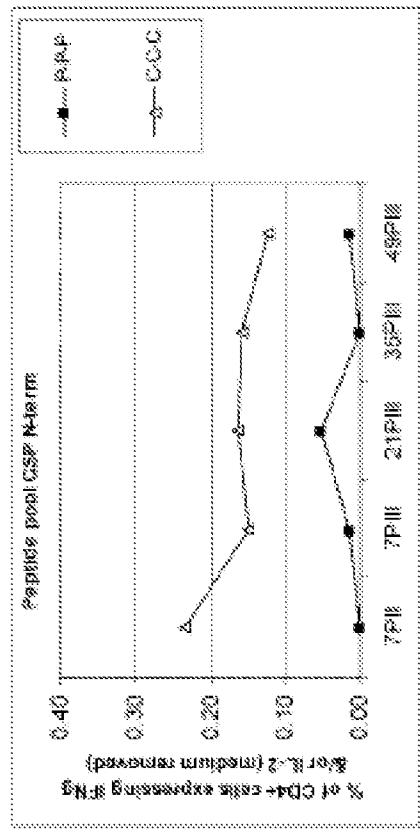
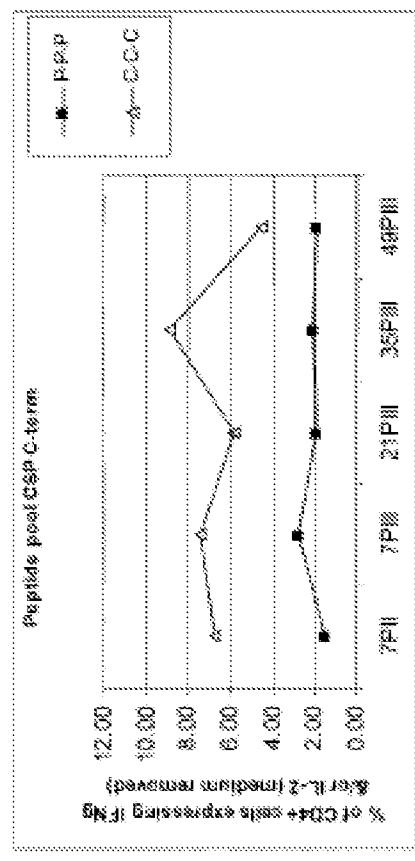


Figure 21



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Figure 22

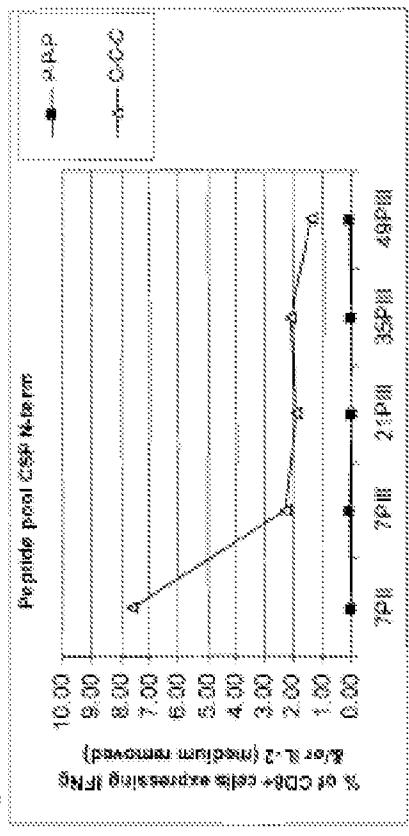


Figure 23

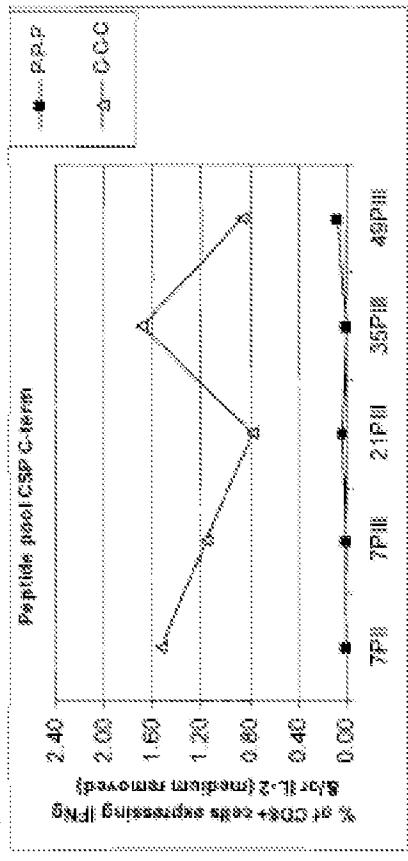
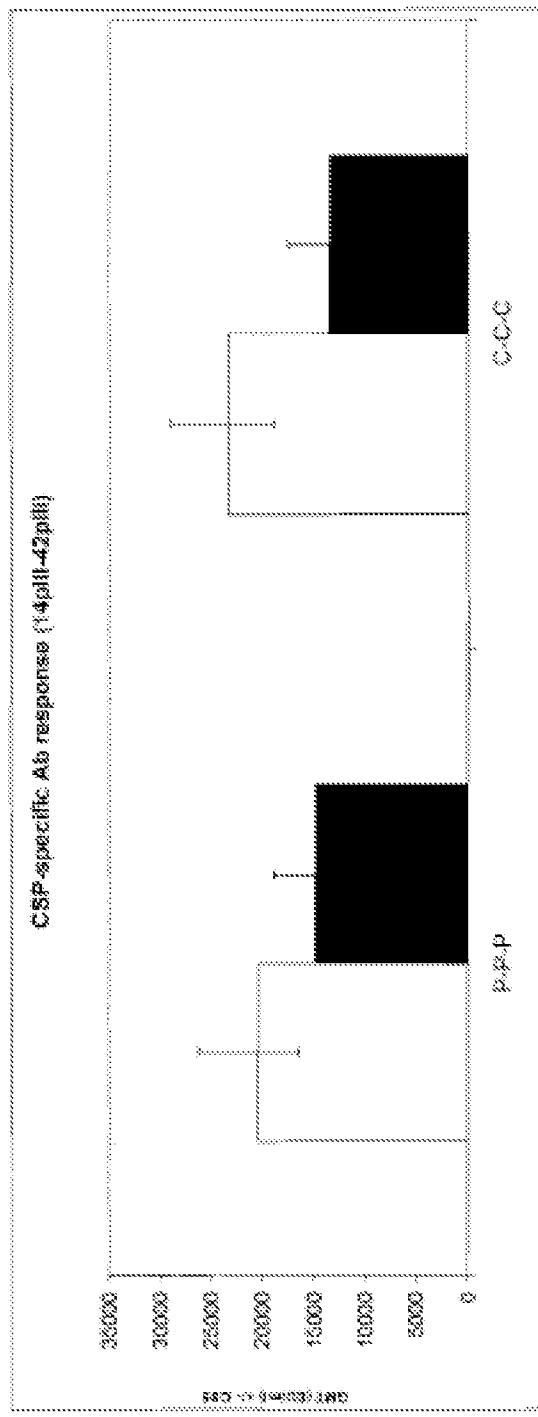


Figure 24  
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2008/052448

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/16 C07K14/445 C12N15/861 A61K39/00

According to International Patent Classification (IPC) or in both national classification and IPC

## B. FIELDS SEARCHED

The following documentation searched (classification system followed by classification systems)  
C07K A61K C12N

Documentation consulted other than literature documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Description of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/110482 A (ISIS INNOVATION [GB]; HILL ADRIAN [GB]; MOORE ANNE C [GB]; NICOLL CLAI) 23 December 2004 (2004-12-23) the whole document	1-15, 19, 28, 34-38, 40
Y		16-18, 20-27, 29-33
Y	WO 02/22080 A (MERCK & CO INC [US]; EMINI EMILIO A [US]; YOUNG RIMA [US]; BETT ANDREW) 21 March 2002 (2002-03-21) page 22, lines 4-17 the whole document	16-18
Y	WO 2006/120034 A (GLAXO GROUP LTD [GB]; ERTL PETER FRANZ [GB]; TITE JOHN PHILIP [GB]; VA) 16 November 2006 (2006-11-16) the whole document	16-18, 20, 22
		-/-



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Specific categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*B\* earlier document but published on or after the international filing date
- \*C\* document which may show design or novelty claimed or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*D\* document referring to an oral disclosure, use, exhibition or other means
- \*E\* document published prior to the international filing date but later than the priority date claimed

\*F\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*G\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*H\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*I\* document member of the same patent family

Date of the actual completion of the international search

29 May 2008

Date of mailing of the international search report

16/06/2008

Name and mailing address of the ISA

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Authorized officer

Irion, Andrea

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/052448

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Character of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/013106 A (GLAXOSMITHKLINE BIOLOGICA SA [BE]; ABRECHT HELGE [BE]; DELCHAMBRE MARTINE) 9 February 2006 (2006-02-09) the whole document	20, 21, 29-33
Y	WO 2007/003384 A (GLAXOSMITHKLINE BIOLOGICA SA [BE]; COHEN JOSEPH D [BE]) 11 January 2007 (2007-01-11) the whole document	23-27, 29-33
Y	GANNE V ET AL: "Enhancement of the efficacy of a replication-defective adenovirus-vectored vaccine by the addition of oil adjuvants" VACCINE, BUTTERWORTH SCIENTIFIC, GUILDFORD, GB, vol. 12, no. 13, 1 January 1994 (1994-01-01), pages 1190-1196, XP002393618 ISSN: 0264-410X the whole document table 1	32

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/EP2008/052446**Box No. II - Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  **Claims Nos.:**  
because they relate to subject matter not required to be searched by the Authority, namely:  

Although claims 1-7, 9-34, 39, and 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  **Claims Nos.:**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  **Claims Nos.:**  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III - Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, the Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention that mentioned in the claim(s) it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/052448

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			CA	2422882 A1		21-03-2002
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			AU	2006245920 A1		16-11-2006
			CA	2608316 A1		16-11-2006
			EP	1880012 A1		23-01-2008
			KR	20080021659 A		07-03-2008
			NO	20075648 B		07-02-2008
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			AU	2005268856 A1		09-02-2006
			BR	PI0514108 A		27-06-2008
			CA	2575398 A1		09-02-2006
			CN	101035897 A		12-09-2007
			EP	1773999 A2		18-04-2007
			JP	2008507987 T		21-03-2008
			KR	20070041765 A		19-04-2007
			US	2007243203 A1		18-10-2007
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			AU	2006265329 A1		11-01-2007
			CA	2613057 A1		11-01-2007
			EP	1896060 A1		12-03-2008